Basic Radiotherapy Physics and Biology

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Second Edition

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Preface

Many radiation oncology textbooks are written in a formal academic style. When studying these highly detailed books, many residents struggle to find a good balance between time and comprehension. *Basic Radiotherapy Physics and Biology* is a by-product of long hours spent in preparation for the American Board of Radiology (ABR) Radiation Therapy Physics and Biology examinations. It is written in a concise and humorous style so that information may be rapidly reviewed, whether for daily use or for exam preparation. Using mnemonics, rules of thumb, and simple figures, we have attempted to make our text as "digestible" as possible. The intended audience for this book includes radiation oncology residents, radiation therapists, dosimetrists, physicists, medical students, and other readers motivated to learn about the physics and biology of radiation therapy.

The topics contained in this book are directly based on the *ABR Radiation Oncology Study Guide* that is available on the ABR website. Whereas the *ABR Study Guides* are formatted as a long list of topics, *this book* is organized into two equal parts. The physics topics are covered in Chaps. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, and 18 and the biology topics are covered in Chaps. 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, and 35. Each chapter consists of a series of concepts explained with bullet points of text, together with figures, equations, and mnemonics where appropriate and concise. A few math-heavy chapters also include a section entitled "Rules of Thumb." These rules intend to summarize mathematical concepts in plain language, favoring ease-of-use over detail. The book also includes two appendices of reference information: a glossary of terms and physical constants and a list of radionuclides used in imaging and radiotherapy.

This book does not cite specific references, as it is a collection of basic rules and principles and not a rigorous scholastic work. Those who wish to delve into the primary literature should refer to one of the many comprehensive textbooks and research papers that already exist. Instead, our book is designed as a quick reference, helpful for exam preparation and daily clinical practice in the real world. It is our hope that this book will be of great value to all students and would-be students in every discipline of radiation oncology.

Preface to the Second Edition

The unanimous decision by all co-authors to prepare a second edition of *Basic Radiotherapy Physics and Biology* was motivated not by the expectation of huge royalties. Nope! Those contemplating writing a textbook are in for a rude awakening if "financial windfall" is the main reason for writing a textbook, especially with 5 co-authors! Instead, we were motivated after receiving consistent positive feedback regarding the utility of the first edition in preparing radiation oncology residents for their board exams in biology and physics, and also by the realization that several of the chapters required an update.

We have endeavored to keep the writing style concise and with sporadic and well-placed injections of humor, so as to preserve the spirit of the first edition. However, with the realization that individualized medicine is here to stay and that cancer therapy will more frequently be guided by molecular tests that reveal genes, proteins, and pathways that can be targeted (or at least potentially targeted) and that residents and students would be expected to know about, we feel we would be remiss if we did not include what we believe to be the relevant players in the relevant pathways, with what we perceive to be the required level of minutiae. Thus, especially in the biology section, if readers were to compare the first and second editions, they would note an enhanced "attention to details" in several of the chapters. For example, the chapter on DNA damage/repair has been extensively updated, and the chapter that covers cell death and survival assays now includes additional sections that highlight other modes of death that now appear to be triggered by ionizing radiation.

Several other chapters were significantly revised. The chapter on effects of acute total body irradiation now includes more information about radiation countermeasures. The chapter in which we cover stochastic versus deterministic effects now includes updated recommendations for annual lens dose limits and current views on classification of cataractogenesis as stochastic or deterministic effect. Also, new content has been added about the exciting areas of immunotherapy and immunomodulation of the radiotherapy response.

Those that use this book to prepare for radiation oncology board exams are still advised to consult the *ABR Radiation Oncology Study Guide,* because content and emphasis can and does change over time. Since the book continues to be a collection of basic rules, principles, and current thinking in the fields of biology and physics, we continue to eschew citation of specific references. It remains a quick (though now somewhat more comprehensive) reference guide for exam preparation and practitioners. We hope that this updated edition will be helpful.

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Part I

Radiation Therapy Physics

Check for updates

Atomic and Nuclear Structure

1

Introduction

The nucleus is the core of the atom and is made up of several nucleons called protons and neutrons that are held together by strong force but also have tension to fall apart by coulombic forces exerted by the protons. The individual nucleons are made up of quarks that are held together by the weak force. Mass and energy are interchangeable by $E = mc^2$, and this can be demonstrated by the nuclear binding energy that causes a mass deficit caused by the nuclear binding energy. Several factors go into determining the stability of a nucleus, including neutron-to-proton ratio, nucleon pairing, and binding energy per nucleon. For the purposes of this book, the Bohr model will be used to describe electron behavior and interactions. This model uses finite energy shells with fixed binding energies. Any transition of an electron into a higher energy shell requires energy absorption (often in the form of a photon), and any transition of an electron into a lower energy shell will result in energy release, either in the form of a characteristic X-ray or in the form of an Auger electron.

Atomic and Nuclear Nomenclature

- The **atom** includes a **nucleus** and **electrons**.
  - Electrons determine the chemical properties of an atom.
  - **Nuclide** refers to the composition of the nucleus (number of protons and neutrons).
  - **Nucleons** include **protons** and **neutrons**.
- **The numbers:**
  - **A = Atomic mass number** (total protons + neutrons).
  - **Z = Atomic number** (total protons).

    Z determines the number of electrons, and therefore the chemical properties of the atom.

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  - **N = Neutrons = A – Z.**
- **The four "isos"**:
  - Isoto**p**e: same number of **protons**, different neutrons.
    Same chemical behavior, different mass, and different nuclear decay properties.
    Ex: ^{125}**I** and ^{131}**I,** both behave like iodine but have different half-lives.
  - Isoto**n**e: same number of **neutrons**, different protons.
    Rarely used.
  - Iso**bar**: same number of **nucleons**, different nuclide (more protons and less neutrons, or vice versa).
    "**bar**" = same mass—think barbell.
    Beta decay (see Chap. 2) and **electron capture** always result in an **isobar**.
    Ex: ^{131}**I** decays to ^{131}**Xe**, which has the same mass number but is a different nuclide and has different chemical properties.
  - Iso**mer**: same **nuclide**, different energy state (excited vs. non-excited)
    Isomers release their energy through **gamma decay** (see Chap. 2).
    Ex: ^{99m}**Tc** decays to ^{99}**Tc**, releasing its excess energy without changing the number of protons or neutrons.

The Four Fundamental Forces

- In order of descending strength, these are:
- **Strong Nuclear Force**:
  - The strongest force in nature; "glues" the nucleus together.
  - Holds the nucleus together, counters the repulsive effect of protons' positive charge.
- **Electromagnetic (Coulombic) Force**:
  - ~1/100 as strong as the strong force.
  - Opposites attract. Electrons are attracted by the positively charged nucleus and are more attracted as they get closer; valence electrons are not strongly attracted and their movements are responsible for nearly all chemical reactions.
  - Protons repel each other within the nucleus but are held in place by the strong force.
- **Weak Nuclear Force**:
  - ~1/1,000,000 as strong as the strong force.
  - Works inside particles (between quarks) and is responsible for radioactive decay.
  - Ex: ^{14}**C** decays into ^{14}**N** when a proton turns into a neutron and a β^-**.**
- **Gravity**:
  - ~1×10^{-39} as strong as the strong force.
  - Not important on the atomic scale.

On Mass

- **Mass** and **energy** are always interchangeable based on Einstein's $\mathbf{E = mc^2}$.
  - Energy can be converted to mass and mass can be converted to energy by multiplying by c^2 (speed of light squared).
  - As particles approach the speed of light, the velocity must remain constant so as the particle gains energy, it actually gains mass.
- There are two common ways to measure **mass**.
- **Atomic mass units (AMU)**:
  - Defined as 1/12 the mass of a Carbon-12 atom.
  - This is slightly less than the mass of the component particles, due to the **binding energy** of the carbon atom (see below).
  - **Proton mass = 1.0073 AMU**.
  - **Neutron mass = 1.0087 AMU** (slightly larger than a proton).
  - **Electron mass = 0.0005 AMU** (approx. 1/2000).
- **Energy equivalent (MeV/c ^{2}**, may be shortened to just "**MeV**"):
  - Defined as the equivalent amount of energy **(mc ^{2})**, measured in mega electron volts.
  - **Proton mass = 938.3 MeV.**
  - **Neutron mass = 939.6 MeV.**
  - **Electron mass = 0.511 MeV** (or **511 keV**).
  - **1 AMU = 931.5 MeV.**

Nuclear Binding Energy

- When particles are bound to each other, they give off energy.
  - Stars shine as they perform fusion (atoms combining) and synthesize nuclei!
  - **Nuclear binding energy** is the energy from binding neutrons and protons into a nucleus.
- This energy is "paid for" in mass, according to **E = mc ^{2}**.
  - This "**mass deficit**" is equal to the **binding energy**.
  - **Ex: Carbon-12** (^{12} **C**) contains 6 protons and 6 neutrons.
    The sum of masses should be **12.09565 AMU**, but ^{12} **C** has a mass of **12.00000 AMU**.
  - The mass deficit is 0**.09565 AMU**, or **89.1 MeV**, and this is the binding energy that holds the nucleus together.
- In order to unbind something, you need to spend at least as much energy as the binding energy.
  - You cannot split a carbon nucleus with 18 MeV photons from an average linac, but you could with a cyclotron throwing 200+ MeV protons.

On Nuclear Stability

- **Neutron-to-proton (n/p) ratio**:
  - Protons generally hate each other due to their charge; they need neutrons to keep the peace.
  - Too many neutrons and the nucleus just becomes uncomfortable.
  - Unstable nuclei will decay toward more stable products. The mode of decay depends on the n/p ratio.

    See Chap. 2 for more detail on nuclear decay.
- For elements up to **Z = 20 (Calcium)**, the magic n/p ratio is **1:1**.
  - **Ex**: Stable carbon (^{12} **C**) has n = 6, p = 6.
- For elements heavier than **Z = 20**, the magic n/p ratio is **>1:1**.
  - **Ex:** Stable gold **(^{197}Au)** has n = 118, p = 79 (Fig. 1.1**).**

Binding Energy per Nucleon

- As atomic number increases, strong force increases and therefore total binding energy increases.
- At the same time, after a certain threshold (**iron, Z = 26**), the repulsive electrostatic force of protons begins to take over (since they hate each other).
  - Even though the total binding energy continues to increase, the binding energy per nucleon starts to decrease.
  - Binding energy must be at least 8.6 MeV per nucleon to remain stable.

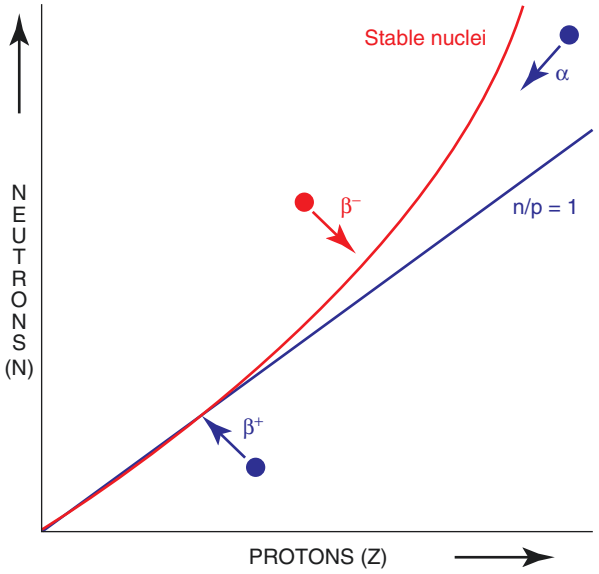

Fig. 1.1 Stable nuclei (*red line*) initially follows a 1:1 ratio of neutrons to protons but gradually requires more nexutrons to keep the nucleus stable

- When atoms are unstable, weak forces allow nucleon transformations (example: a proton may turn into a neutron).
- Unstable atoms larger than Tellurium (Z = 52) may break off in large chunks (usually in even numbers such as alpha particles).
- **Bismuth (Z = 83)** is the heaviest stable nucleus, after which total binding energy decreases and all nuclei become unstable.

Pairing of Nucleons

- Paired nucleons are generally more stable than odd-numbered ones.
  - Most stable nuclei are "even-even," with an even number of protons and an even number of neutrons.
  - A few stable nuclei are "odd-even" or "even-odd."
  - Only four stable "odd-odd" nuclei exist: **H-2** (1n, 1p), **Li-6** (3n, 3p), **B-10** (5n, 5p), and **N-14** (7n, 7p).
- For this reason, it is much easier to emit an alpha particle (2n, 2p) than a lone neutron or proton in heavier nuclei.

Bohr Model of the Atom

- This is the "classical" description of electrons orbiting the nucleus such as planets around the sun (Fig. 1.2).

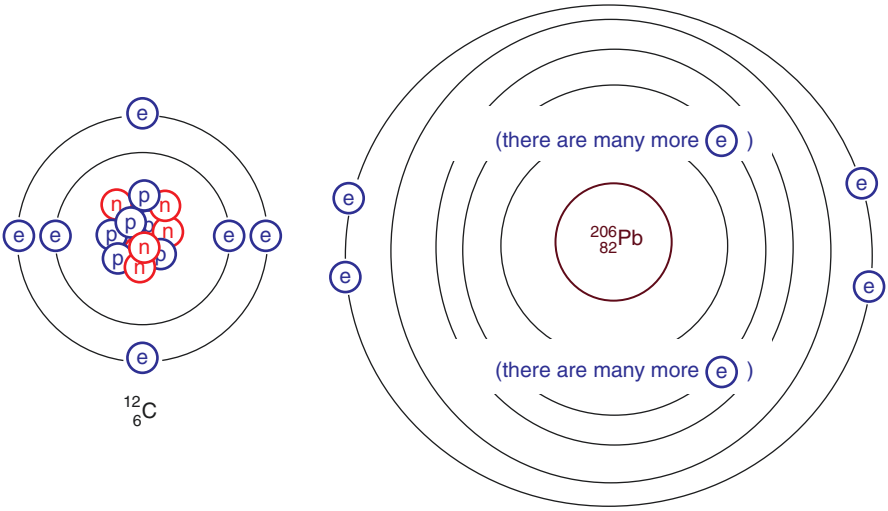

Fig. 1.2 Bohr model of the atom has a nucleus (like the sun) with electrons revolving around it (like planets). As electrons are added, they fill higher energy orbitals (further away from the nucleus) in fixed paths

  - Within an atom, electrons may only travel in discrete orbits (energy shells) with discrete energies.
  - Electrons may only gain or lose energy by changing orbits or by exiting the atom.
  - This model works great for a hydrogen atom (and for the ABR exam), but it is a gross oversimplification of the more accurate quantum mechanical model.
- **Electron binding energy**:
  - Electrons are bound to the nucleus by the attraction between negative and positive charges.
  - This attraction means that it takes energy from outside to separate the nucleus from the electron.
    Electron binding energy (the energy required to knock an electron loose) increases with proximity to the nucleus by radius squared (r^2).
    Electron binding energy increases with increasing charge of the nucleus (Z).
  - Inner shell electrons have a large binding energy because they are very close to the nucleus.
    Even though they have a higher "binding energy," these electrons are said to be at a "lower energy level."
  - Valence (outer) electrons have little binding energy because they are further away and are easily removed.
- Any change in orbit is associated with a change in energy (see section "Electron Transitions").
  - Pushing energy into an atom can knock an electron loose from its valence shell (or raise the shell to a higher shell).
  - When an electron moves from a higher shell to a lower shell, it actually gives off energy, either in the form of a photon or by kinetic energy and knocking another electron to a higher shell.

Electron Orbits (Energy Levels)

- Each electron fits into energy levels in an orderly fashion with a particular address.
- **Principle quantum number** (n) = 1, 2, 3, etc. or K, L, M, N, etc.
- **Orbital quantum number** (l)—can have (n − 1) values.
  - Named s, p, d, f for sphere, peanut, dumbbell, fan.
  - Ex: if n = 3, then there are l orbitals 0,1,2.
- **Magnetic quantum number** (m_l)—can have $2l + 1$ values.
  - Numbered negative (n − 1) through positive (n − 1).
  - Ex: n = 3, $l = 2$, therefore m_l can be −2,−1,0,+1,+2.
- **Spin quantum number**—for our purposes, either +1/2 or − 1/2.
- **Outer (valence) shell** can have up to eight electrons.
  - These are generally s^2 and p^6.

Electron Transitions (Absorption and Emission of Energy)

- Whenever an electron absorbs energy, it becomes uncomfortable.
  - The electron may move to a higher shell, or it may be ejected from the atom.
  - If an electron moves to a lower energy shell, excess energy may be carried away as the electron's kinetic energy, or it may be emitted as a photon (Fig. 1.3).
- When a vacancy exists in a lower shell, an electron will "fall" into a more comfortable position.
  - The electron loses energy, so this energy must be transferred to some other particle.
  - When energy is transferred to a photon, it is known as a **characteristic X-ray**. This is known as "characteristic" because the energy levels are unique to a given nuclide and orbital.
  - When energy is transferred to another electron, it becomes an **Auger electron**. The energy of the **Auger electron** is equal to the energy transferred minus the binding energy that had to be overcome in order to eject an electron (Fig. 1.4).

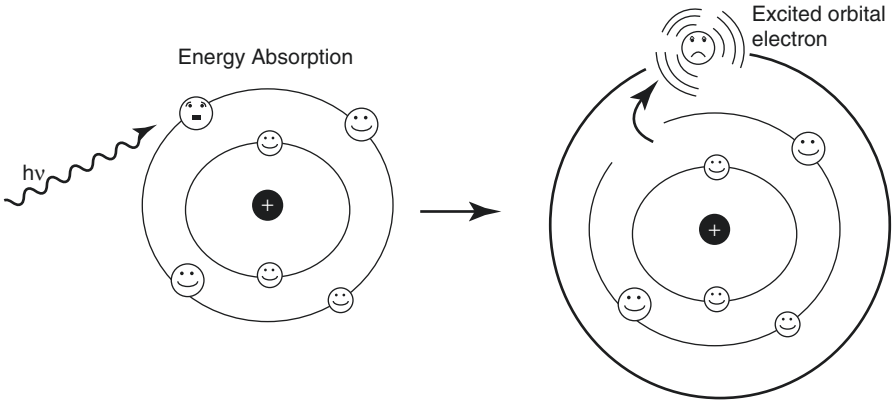

Fig. 1.3 Energy absorption: There is a relatively content orbital electron (it is not as happy as the inner circle electrons). There is an unpleasant orbital above his head that is empty and has a lower binding energy. The orbital electron is hit square in the jaw with a photon containing an intermediate amount of energy, and it absorbs the entire amount and therefore is knocked into a higher orbital. Had he absorbed energy higher than his binding energy, it might have been knocked completely out of the atom (ionization)

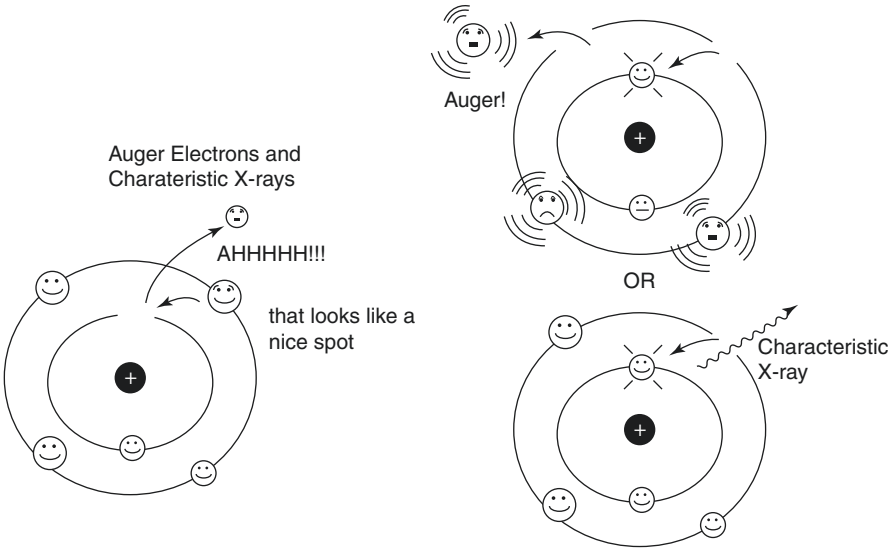

Fig. 1.4 Energy emission consequences: Somehow, a very happy electron was kicked out of the inner orbital and completely disappeared (many things can cause this). An ambitious electron in a higher energy orbital decided to move closer to the nucleus which had a lower energy level (higher binding energy). Since it moved to a lower energy level, it had to give up some of that energy. There are two ways that an electron can give off energy when it drops to a lower energy level. It can emit a **characteristic X-ray** (basically the opposite of Fig. 1.3), or it can transfer that energy to the entire orbital, which makes everyone in the orbital angry until they actually kick out another electron (called an **Auger electron**)

Check for updates

Radioactive Decay

2

Introduction

When atoms become unstable, they undergo changes called radioactive decay. If the nucleus is very heavy and has too many protons, it may undergo alpha decay (release a helium nucleus). If a nucleus is very light and proton heavy, it will undergo either positron emission or electron capture. If a nucleus is neutron heavy, it will likely undergo beta-minus decay. Whenever any of these decay schemes result in an excited nucleus, the nucleus may resume stability by releasing its energy as a gamma ray or by performing an internal conversion, transferring its energy to an electron. The activity of these decay schemes can be described mathematically by using decay constants and natural log functions. These equations can also be used to derive the half-life and mean life of a particular radioisotope. When there are many steps in a decay scheme, the balance between amounts of the various radionuclides can reach various states of equilibriums including transient equilibrium and secular equilibrium. Some radionuclides can be found in nature while others can be created through particle bombardment or nuclear fission.

Definitions

- **Alpha (α) particle**: a particle emitted by the nucleus through α decay, containing two protons and two neutrons.
  - Identical to a helium nucleus.
- **Beta (β) particle**: a particle emitted by the nucleus through **β decay**, either negatively or positively charged.
  - **β^- particle**: basically an electron but from the nucleus ("negatron," normal matter).
  - **β^+ particle**: a positron (antimatter, positively charged version of electron).
- **Gamma (γ) ray**: a photon emitted by the nucleus (different from an X-ray that is from an electron interaction but may have the same energy range).

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  - **Internal conversion electron**: emitted when a nucleus transfers energy to an orbital electron instead of emitting a gamma ray.
- **Characteristic X-ray**: a photon emitted by an electron transitioning from one shell to another.
  - Other than the source of production, a 30-keV X-ray is identical to a 30-keV $\gamma-$ray.

Formalism: Decay Schemes

- Radioactive decay may be described by a reaction scheme, such as:

$$^{226}_{88}\mathrm{Ra} \xrightarrow[1{,}622y]{T_{1/2}} {}^{222}_{86}\mathrm{Rn} + {}^{4}_{2}\mathrm{He} + 4.87\ \mathrm{MeV} \tag{2.1}$$

- These schemes allow us to track mass, charge, and energy.
  - Mass, charge, and energy are always conserved. In order to gain charge, a nucleus must emit a negative charge and the like.
- Decay energy is shared between the decay products, depending on the mode of decay.
  - In **α decay**, almost all of the energy goes into the α-particle.
  - In **γ decay**, all of the energy goes into the photon (or an internal conversion electron, in internal conversion).
  - In **β decay**, energy is shared between a beta particle and a neutrino or an antineutrino.

Alpha (α) Decay

- **The nucleus is bloated, proton heavy, and wants to lose weight**!
  - The "pairing rule" states that particles are more stable in pairs.
  - Therefore, nuclei emit alpha particles (two neutrons and two protons) instead of single protons or neutrons.
- Occurs in very heavy ($Z > 52$) nuclei, such as:

$$^{226}_{88}\mathrm{Ra} \xrightarrow[1{,}622y]{T_{1/2}} {}^{222}_{86}\mathrm{Rn} + {}^{4}_{2}\mathrm{He} + 4.87\ \mathrm{MeV} \tag{2.2}$$

- Decay energy is split between the daughter nucleus and the alpha particle, but almost all of it goes to the alpha particle.
  - Typical alpha energies range from **2 to 8 MeV**.
  - Alpha particles are **monoenergetic**.

Beta (β) Decay

- Occurs in nuclei that need to gain or lose protons, such as:

$$^{32}_{15}\mathrm{P} \underset{14.5d}{\overset{T_{1/2}}{\rightarrow}} {}^{32}_{16}\mathrm{S} + {}^{0}_{-1}\beta + \tilde{\nu} + 1.7\ \mathrm{MeV} \tag{2.3}$$

- Beta decay is always **isobaric** (see Chap. 1), meaning there is no change in atomic mass number.
  - Unlike alpha decay, there is only minimal mass change.
- There are three different beta decay modes:
  - Beta-minus and beta-plus actually produce beta radiation.
  - Electron capture is a "beta" process but produces gamma radiation.
- Beta particles are **polyenergetic** because the energy is shared between the beta particle and the neutrino/antineutrino.
  - Neutrinos and antineutrinos do not really interact with regular matter, so they do not contribute to radiation dose.
  - The average energy of a beta particle is approximately one-third of the maximum energy.

Beta-Minus (β⁻) or Negatron Emission

- **The nucleus is proton-poor and wants more protons**!

$$^{32}_{15}\mathrm{P} \underset{14.5d}{\overset{T_{1/2}}{\rightarrow}} {}^{32}_{16}\mathrm{S} + {}^{0}_{-1}\beta + \tilde{\nu} + 1.7\ \mathrm{MeV} \tag{2.4}$$

- Thanks to weak nuclear force interactions, one of the neutrons is able to turn into a proton.
  - Atomic number goes up by 1; mass stays the same.
- In doing so, the nucleus spits out an **electron** and an antineutrino.
  - The electron is also known as the **β⁻ particle** or **negatron**.
  - When you create matter (**β⁻**), you also create antimatter (antineutrino).

Beta-Plus (β⁺) or Positron Emission

- **The nucleus is proton-rich and wants more neutrons**!

$$^{18}_{9}\mathrm{F} \xrightarrow[110\,\mathrm{min}]{T_{1/2}} {}^{18}_{8}\mathrm{O} + {}^{0}_{+1}\beta + \upsilon + 0.63\ \mathrm{MeV} \tag{2.5}$$

- One of the protons turns into a neutron, basically the exact opposite of beta-minus decay.
  - Atomic number goes down by 1; mass stays the same.
- It spits out an anti-electron (**positron**) and a neutrino.
- **Positrons** are antimatter with mass! When the positron meets a regular electron, it annihilates!
  - This releases the electron and positron's mass as energy.
  - The rest mass of an electron is **0.511 MeV**; so two identical **0.511 MeV** photons are emitted in opposite directions. This is useful for imaging (PET scans).
- Since the positron carries **1.02 MeV** of annihilation energy, it costs **1.02 MeV** to make the positron.
  - Therefore, the kinetic energy is 1.02 MeV less than if the particle had decayed by electron capture.

Electron Capture (EC)

- **The nucleus is proton-rich and wants more neutrons**!

$$^{125}_{53}\mathrm{I}\ {}^{0}_{-1}e \xrightarrow[59.4\,d]{T_{1/2}} {}^{125}_{52}\mathrm{Te} + \upsilon + 35.5\ \mathrm{keV} \tag{2.6}$$

- When nucleus is proton-rich but does not have an excess of 1.02 MeV, **the nucleus eats one of its electrons**.
  - During electron capture it emits a neutrino, but most of the decay energy remains in the daughter nucleus.
  - This energy is immediately emitted as a **gamma ray** or as **internal conversion electrons**.
    (see section "Gamma Emission")
- Proton-rich nuclei with insufficient energy to produce a positron can **only** decay by electron capture.
  - More energetic nuclei can decay by either **beta-plus** or **EC**.
- Because there is a vacancy in one of the inner electron shells, one of the outer shell electrons will fall into this vacancy and produce **characteristic X-rays** or **Auger electrons**.
  - Electron capture with internal conversion results in two electron vacancies! (Fig. 2.1)

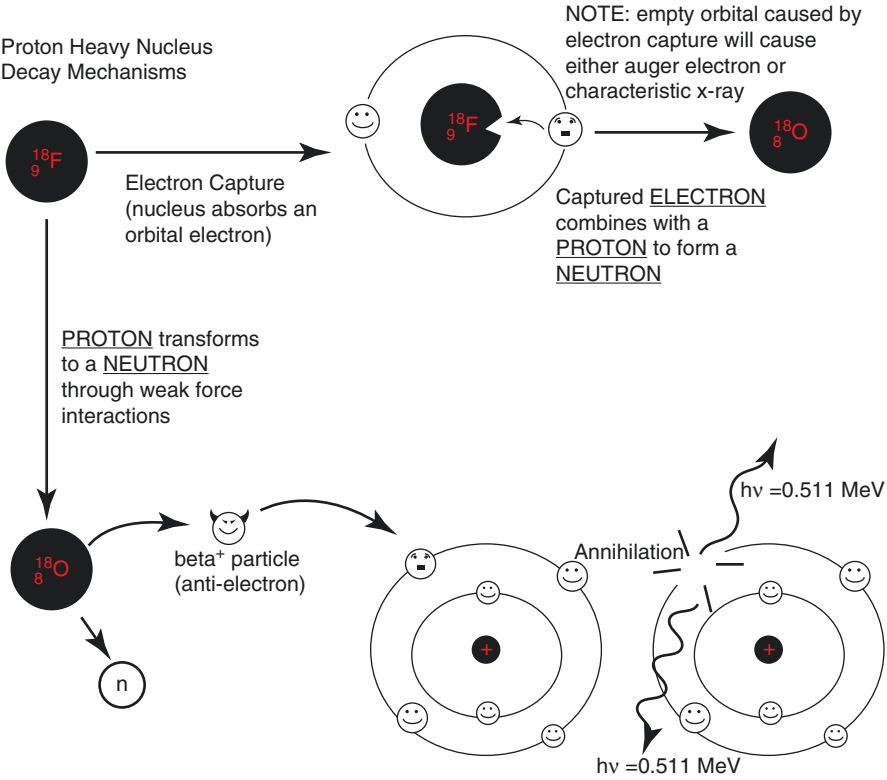

Fig. 2.1 Decay mechanisms of a proton-heavy nucleus: if a nucleus has too many protons or not enough neutrons, the weak forces will allow a proton to actually change into a neutron. The total charge must remain neutral, so this can be accomplished either by eating an electron or by releasing a positron (the evil anti-electron). If electron capture occurs, the nucleus takes a proton and an electron combined to make a neutron. This leaves a hole in a lower energy electron shell and will lead to either characteristic X-rays or an Auger electron being emitted (see Fig. 1.4). If positron emission occurs, there will also be an annihilation reaction when the positron meets an electron producing two gamma rays of 0.511 MeV

Gamma Emission

- **The nucleus is excited and wants to settle down**!
  - Excess energy is released as a **photon**.
- Gamma emission is always **isomeric** (no change in atomic mass or atomic number).
- Most gamma emission occurs during or after alpha or beta decay:
  - When the nucleus is excited, it gets rid of energy through gamma emission or internal conversion.
- For example, ^{60}**Co** decays to an excited ^{60}**Ni**, which immediately releases the excess energy as $\boldsymbol{\gamma}-$rays.

$$\begin{aligned} &{}^{60}_{27}\mathrm{Co} \xrightarrow[5.27y]{T_{1/2}} {}^{60}_{28}\mathrm{Ni} + {}^{0}_{-1}\beta + \tilde{\nu} + 0.31\ \mathrm{MeV} \\ &+1.17\ \mathrm{MeV}\ (\gamma) + 1.33\ \mathrm{MeV}\ (\gamma) \end{aligned} \tag{2.7}$$

– The $\beta-$rays are negligible (they do not escape the machine head) so we call **^{60}Co** a gamma emitter with two photon energies of 1.17 and 1.33 MeV (average 1.25 MeV).

- **Metastable** nuclear isomers such as **^{99m}Tc** can exist in an excited state and emit gammas more gradually:

$$ {}^{99m}_{43}\mathrm{Tc} \xrightarrow[6.0h]{T_{1/2}} {}^{99}_{43}\mathrm{Tc} + 140.5\ \mathrm{keV} \tag{2.8}$$

Internal Conversion

- **The nucleus is excited and it kicks out an electron**!
  - Instead of releasing excess energy as a photon, the nucleus transfers that energy to an inner shell electron.
  - This electron is **not** a beta particle. It does not emerge from the nucleus; it is a preexisting electron.
- For example, **^{125}I** decays by electron capture with energy of **35.5 keV** (see above).
  - Most of the time, it releases internal conversion electrons instead of gamma rays.
  - If **35.5 keV** is used to eject an electron with a binding energy of **8.5 keV**, the electron is emitted at **27 keV**.
  - Since different electrons have different binding energies, IC results in a spectrum of energies.
- This produces a vacancy in an inner electron shell. Outer shell electrons will fill the vacancy, producing **characteristic X-rays** or **Auger electrons** (see Chap. 1).
  - The useful radiation from a **^{125}I** brachytherapy seed is actually **characteristic X-rays** (Fig. 2.2).

Mathematics of Radioactive Decay

- **Units of activity**:
  - **1 Curie (Ci)** = 3.7×10^{10} disintegrations per second.
  - **1 Becquerel (Bq)** = 1 disintegration per second.
  - The **Bq** is the SI unit, but the **Ci** is commonly used in the clinic.
- **Exponential decay**:

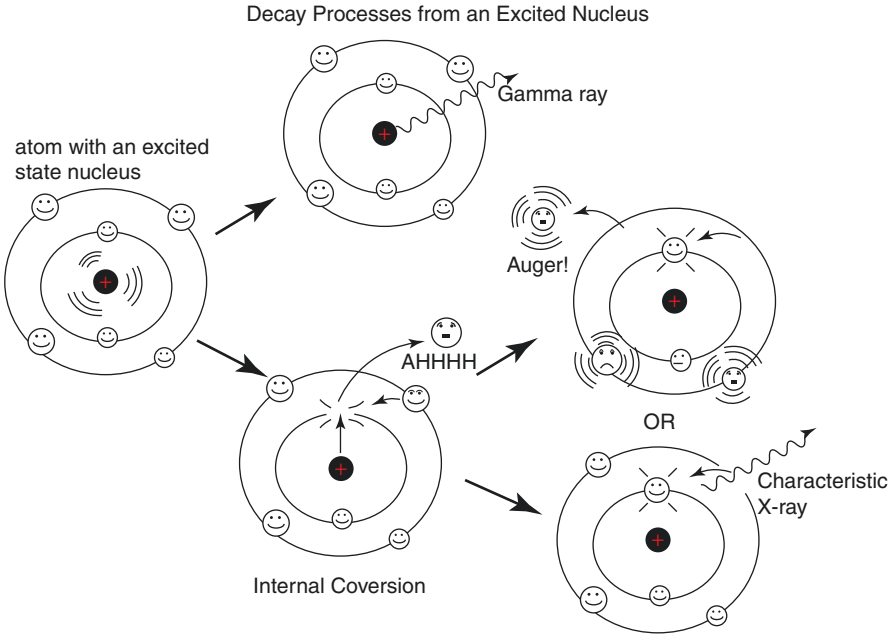

Fig. 2.2 Decay processes from an excited nucleus: when a nucleus is in an excited or metastable state (usually from a previous nuclear reaction like beta emission), it can get rid of that extra energy by two main mechanisms: **Gamma emission** and **Internal conversion**. In gamma emission, the excess energy is simply released as a photon (gamma ray) with the exact amount of energy needed to become stable. In internal conversion, all that energy is transferred to a low-energy orbital electron, and it is ejected from the atom (this is very similar to the photo-electric effect in Chap. 4). Once a nice new slot has opened up, a higher energy electron is free to take the nice new comfortable spot and will either cause a characteristic X-ray or transfer the leftover energy to an Auger electron (see Fig. 1.4)

– Activity (A) is proportional to number of atoms present (N), multiplied by the decay constant **λ**. The decay constant is unique to each radionuclide.

$$A = -\lambda N \tag{2.9}$$

– Atoms decay over time as a mathematical function of the natural log (e) raised to the power of its unique decay constant multiplied by time; therefore, atomic decay over time is expressed as follows:

$$A(t) = A_0 e^{-\lambda t} \tag{2.10}$$

- **Half-life**: how long it takes to decay to half the original activity:

$$t_{1/2} = \frac{\ln 2}{\lambda} = \frac{0.693}{\lambda} \tag{2.11}$$

  - Nuclides with a long half-life have a low activity, and vice versa. Think of hot fast-burning nuclei versus slow smoldering nuclei.

- **Mean life**: defined quite simply as 1/λ:

$$\tau = t_{\text{avg}} = \frac{1}{\lambda} = 1.44 \times t_{1/2} \tag{2.12}$$

  - This is equal to the hypothetical amount of time it would take a source to completely decay, if it decayed at a constant rate equal to its initial activity (which never happens).
  - Mean life is useful for calculating dose and dose rate of permanent brachytherapy implants (see Chap. 11).

- **Effective half-life**: when an isotope is being excreted from the body, its half-life is shorter than its physical half-life.
  - If $\mathbf{t_p}$ is the physical half-life, and $\mathbf{t_b}$ is the biological (excretion) half-time, then $\mathbf{t_{eff}}$ is the effective half-life:

$$\frac{1}{t_{\text{eff}}} = \frac{1}{t_b} + \frac{1}{t_p}; \boldsymbol{t}_{\text{eff}} = \frac{\left(t_b \times t_p\right)}{\left(t_b + t_p\right)} \tag{2.13}$$

Radioactive Equilibrium

- Sometimes there are multiple radioactive species in sequence, each with its own half-life. If placed in a sealed container, these may reach "equilibrium" over time.
  - For example, a radium source contains ^{226}**Ra** that decays to ^{222}**Rn** that decays to further radionuclides.
  - The first nuclide in the decay chain is called the **parent**, while the second nuclide is the **daughter**.
- **Secular equilibrium**: when daughter half-life is **much** shorter than the parent half-life.
  - The daughter activity builds up over time, until it is roughly equal to the parent activity.
  - You can only produce the daughter nuclide as fast as the parent will decay, so the activity (disintegrations per second) is bottlenecked at the first step.

After the buildup period, the apparent activity and half-life of the daughter are basically the same as the parent.

  - **Examples**:
    ^{226}Ra (half-life 1,620 years) → Rn-222 (4.8 days).
    ^{222}Rn is much more active than **^{226}Ra**.
    Radium needles are composed of a platinum tube full of radium salts that decay into radon gas that is trapped in the tube. The radon delivers the actual gamma radiation.
    ^{90}Sr (half-life 29.12 years) → ^{90}Y (64 h).
    ^{90}Sr applicators may be used by themselves (such as in eye plaques), or the **^{90}Y** may be extracted for further use (such as in radioactive microspheres).

- **Transient equilibrium**: when daughter half-life is only a little shorter than the parent half-life.
  - The daughter activity builds up as the parent activity decays.
  - Eventually the daughter activity slightly exceeds the parent activity, and both curves decay together.
  - During transient equilibrium, the daughter nuclide appears to have slightly more activity and the same half-life as the parent.
  - **Example:** heart scans use ^{99m}Tc (metastable technetium), which comes with love from the "Moly cow," born and raised at your friendly neighborhood nuclear reactor.
  - **^{99}Mo (half-life 66 h) → ^{99m}Tc (6 h)**.
  - Note: ^{99}Mo sources really are called cows.
  - A radionuclide generator regularly "milks" the Tc-99 m from the "cow" ^{99}Mo.
  - Each time this occurs, there is another gradual buildup of Tc-99 m and the new transient equilibrium is reached where it is theoretically slightly higher than that of ^{99}Mo.
  - Actually it never quite surpasses ^{99}Mo because the production efficiency is about 88%.
- **No equilibrium**: when daughter half-life is longer than parent half-life.
  - All of the parent nuclide decays into daughter, and there is no equilibrium.
  - **Example: ^{131}Te** (30 h) → **^{131}I** (192 h).

Daughter Elution

- When the daughter nuclide is extracted from a parent for use (i.e., ^{99m}Tc, ^{90}Y), it is called "daughter elution" or "milking the cow."
  - This is useful for tabletop production of a short half-life nuclide.
- Every time the daughter is removed from the parent, there is another buildup period: parent nuclide produces daughter nuclide until they reach either secular or transient equilibrium.

Naturally Occurring Radioisotopes

- These are mostly atomic numbers 81–92 in four series plus some weird ones.
- **Thorium series** (4n).
- **Neptunium series** (4n + 1).
- **Uranium series** (4n + 2), (most important)—starts with ^{238}U and includes ^{226}Ra and ^{222}Rn.
- Actinium series (4n + 3).
- **Oddballs** (not part of a well-defined decay series).
  - ^{3}H, ^{14}C (carbon dating), ^{40}K (bananas), ^{50}V, ^{87}Rb, ^{115}In, ^{130}Te, ^{138}La, ^{142}Ce, ^{144}Nd, ^{147}Sm, ^{176}Lu, ^{187}Re, ^{192}Pt

Man-Made Radioisotopes

- **Nuclear bombardment**—stable nuclei may be bombarded with protons, neutrons, or other particles to get new radioactive species.
  - **Neutron bombardment**—the longer a neutron hangs around a nucleus, the higher the probability of causing a nuclear reaction, therefore neutrons need to be slow or "thermal" with energy around 0.025 eV. There are four main neutron reactions.

    (n, γ)—most common—nucleus absorbs a neutron, gets excited, and releases a gamma ray.

    Example: $^{1}\mathrm{H} + \mathrm{n} \rightarrow {}^{2}\mathrm{H}$ (hydrogen bombarded with a neutron becomes deuterium).

    (n, α)—neutron goes in, alpha particle (helium nucleus) breaks off from nucleus.

    Example: $^{10}\mathrm{B} + \mathrm{n} \rightarrow {}^{7}\mathrm{Li} \pm {}^{4}\mathrm{He}$ (this reaction is the basis for neutron detection).

    (n, p)—neutron goes in, proton is kicked out (no neutron to proton transformations).

    Example: $^{32}\mathrm{S} + \mathrm{n} \rightarrow {}^{32}\mathrm{P} + {}^{1}\mathrm{H}$ (this is how you make ^{32}P for craniopharyngioma treatments).

    Fission!!!—see below.
  - **Charged particle bombardment**

    Protons—throwing protons at something will often create positron emitters (such as ^{18}F used in PET scans) but can also cause other reactions noted below.

    (p, γ)—proton goes in, excite nucleus, and gamma rays come out.

    (p, n)—proton goes in, neutron gets kicked out.

    (p, d)—proton goes in, deuteron (^{2}H) gets kicked out.

    Heavier particles—alpha particles (^{4}He nuclei) and deuterons (^{2}H nuclei) can also be used—both are capable of being incorporated into the nucleus with the end result being the expulsion of a proton or a neutron.
- **Fission—NUKES**!

- ^{235}U or ^{239}Pu absorbs a thermal (slow-moving) neutron and splits, usually into two major products of unequal masses around 90–100 and 130–140, plus additional neutrons or smaller nuclei, and a lot of energy.
  Most sources show ^{235}U splitting into ^{92}Kr and ^{141}Ba with 3 neutrons and 200 MeV.
- ^{238}U makes up 99.2% of natural uranium, is less likely to undergo fission, and will not sustain a chain reaction even if it does.
- Uranium enrichment increases the percentage of ^{235}U to increase the ability to sustain fission.
  Low enriched (3–4% ^{235}U) is used for power plants, and some can even use un-enriched uranium.
  Nuclear weapons require at least 20% ^{235}U with special engineering; most developed countries use around 80–90% ^{235}U, or plutonium.
- When a fission reaction takes place, it releases neutrons that can cause another fission reaction. The chain reaction can sustain itself if it reaches "critical mass."
  For nuclear power plants, you try to control this by absorbing some of the neutrons with boron, cadmium, or water but in a weapon, you just let the reaction go nuts.
- Nuclear reactors are used to make MANY of our sources: **^{90}Sr, ^{90}Y, ^{131}I (NOT ^{125}I or ^{123}I), ^{89}Sr, ^{192}Ir, ^{60}Co, ^{137}Cs**.

See Appendix B for a complete list of nuclides.

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Production and Properties of Radiation

3

Introduction

Electromagnetic radiation is used in radiation therapy for its unique properties and relative ease of production compared to other forms of particle radiation. Particles are directly ionizing while electromagnetic radiation is indirectly ionizing because it sets other particles in motion to deposit the dose. The majority of innovation in radiation therapy has focused on electromagnetic radiation, beginning with X-ray tubes and γ-rays emitted from man-made radioisotopes. Later on, with the development of the waveguide and accelerator tube came the linear accelerator and the microtron, which offered the ability to deliver photons and electrons in the megavoltage energy range. More recently, electromagnets were developed to be powerful enough to accelerate heavier particles to extremely high energies in a cyclotron or a synchrotron for particle beam therapy.

Definitions

- **A** = Amplitude of a wave
- ν = Frequency of a wave
- λ = Wavelength of a wave
- p = Momentum of a particle
- h = Planck's constant = 6.62×10^{-34} J s
- c = Speed of light = 3×10^{8} m/s
- **Bremsstrahlung**: "braking radiation"; photons that are produced whenever a fast-moving electron slows down near nucleus.
- **kilovolts peak** (**kVp**): maximum accelerating voltage of an X-ray tube.

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Particulate Radiation

- Particles include electrons, protons, carbon ions (and other ions), pions, and whatever else comes out of big accelerators such as CERN.
  - Photons and other bosons are NOT considered particles for the purpose of radiation therapy as they are considered carriers for forces – in the case of photons, electromagnetic force.
- Relativistic energy equation – all particles must obey the law $E = mc^2$; therefore, as you increase the energy for particles already at 99.9% of the speed of light, the mass increases (note that the particles get heavier but not larger in size).
- The resting mass of a particle can be converted to pure energy if you destroy it.

Electromagnetic (EM) Radiation

- Carried by photons (a type of boson).
- Wave-particle duality – EM radiation can be either a wave or a particle (photons) depending on how you look at it. Actually, everything can be described as both, but photons are extra special because they carry electromagnetic force in the form of two sine waves (electric field and magnetic field) that are perpendicular to each other (Fig. 3.1).

Wave Equations

$$A = A_0 \sin\left(2\pi\upsilon t\right) \tag{3.1}$$

$$\upsilon = {}^{c}\!/_{\lambda} \tag{3.2}$$

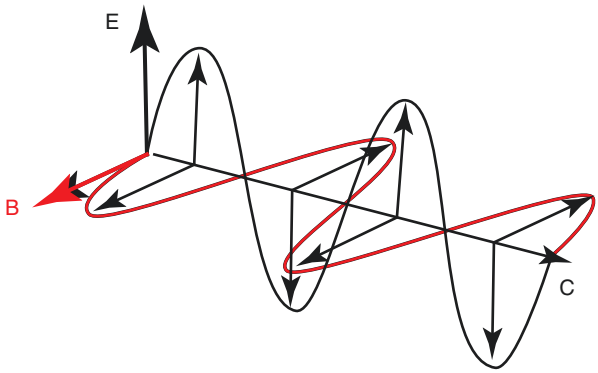

Fig. 3.1 Electromagnetic radiation wave form: there is an electrical sine wave (*Black* "E") and a magnetic sine wave (*Red* "B") that are perpendicular to each other

- This means that you can always interchange **ν** and **λ** by dividing the speed of light (c) by the other term.
- Photons possess momentum by $p = h\,\nu/c$, where **c** is the speed of light, h is Planck's constant, and **ν** is frequency (we never use this).
- Photons possess energy by $E = h\,\nu$ (we use this a little more often).
- Since **h** and **c** are constants, we can rearrange and simplify everything to say electromagnetic wave length and energy are connected as:

$$E\ (\mathrm{keV}) = \frac{1.24}{\lambda\ (nm)} \tag{3.3}$$

Electromagnetic Spectrum (Remember This from Fourth Grade?)

- In order of increasing energy: radio waves → microwaves → infrared → rainbow colors, light → UV rays → X-rays, gamma rays, and cosmic rays.
- **Here are a couple of valuable points**:
  - EM radiation actually becomes **ionizing** in the **extreme UV spectrum** since the ionization threshold for a hydrogen atom is 13.6 eV and higher (91.2 nm wavelength and smaller).
  - X-rays are **>124 eV** (around 10 nm) and therefore well above the energy threshold to cause ionizations.
  - By definition, **X-rays** come from electron interactions, **γ-rays** come from the nucleus (like the difference between electrons and beta particles).
  - They can have the same energies but are named based on their origin.
- As a side-note, UV radiation can still cause chemical reactions by exciting valence electrons, altering chemical bonds without actually ionizing. This is why sun-tanning is bad and still cancer-causing even though there is no "ionizing" radiation involved.

Production of Radiation

- **Radioactive decay** – for full details, see Chap. 2.
- Photons can be produced by the nucleus (**γ-rays**, **e.g.,** ^{60}**Co**) or by interactions of electron orbitals (**X-rays**, **e.g.,** ^{125}**I**).
- Electrons may be ejected as **Auger electrons** or as **beta particles**.
- Alpha particles are produced by radioactive decay of heavy nuclei.

X-Ray Tube

Diagnostic Energies

- Used for plain X-ray imaging, mammography, CT scans, and so on.
- **Bremsstrahlung X-rays** are produced whenever fast-moving electrons interact with matter.
  - An **X-ray tube** must first accelerate the electrons, in order to make X-rays through Bremsstrahlung.
  - **Electrons are produced**:
    A **cathode** (usually a tungsten wire) is heated, liberating electrons via **thermionic emissions**. These electrons float around the filament in a sort of cloud.
  - **Electrons are accelerated**:
    The **slow-moving cloud of electrons must be accelerated by a very high-voltage electric field in a vacuum (must be a vacuum or else the electrons will collide with molecules).**
    Acceleration potential is measured in kilovolts (kV).
    Electrons travel from the cathode to the anode, accelerating between 50% and 99% of the speed of light!
  - **Electrons are decelerated**:
    The fast-moving electrons run into a target that is in front of the anode. The **electrons have their paths bent and slowed down by high-Z material** (*tungsten* or molybdenum), which produces Bremsstrahlung radiation (Fig. 3.2).

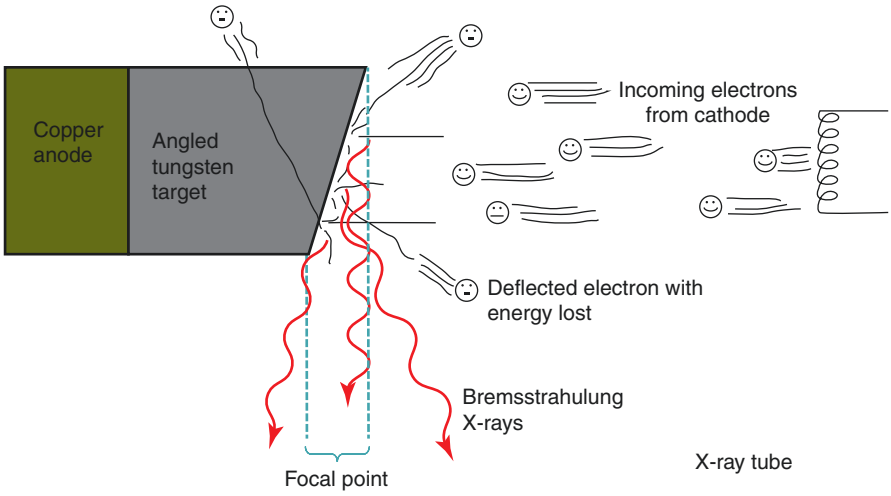

Fig. 3.2 X-ray tube: electrons are created at a hot filament that acts as a cathode. The electrons then are attracted toward the positively charged copper anode and strike the tungsten target that is placed in front of it. Whenever electrons slow down, crash, or change their course, they emit bremsstrahlung X-rays. The tungsten target is angled in such a way that the majority of the bremsstrahlung X-rays are directed in a specific direction. The angle of the target affects the width of the focal point from which the X-rays generally originate. For imaging purposes, you want as small of a focal point as possible while still being able to deflect X-rays in the proper direction

Side Notes

- This process is extremely inefficient since around **99% of the energy is converted to heat**. X-rays may go in any direction, including into the tungsten target where they get absorbed and do nothing.
- By setting the target at a slight angle (7–18°), you can create a **small focal spot** where X-rays preferentially come out at a right angle to the incident electron beam. You want as small a focal spot as possible (0.3–3 mm) for good image quality.
- **kVp**: peak kilovoltage potential in an X-ray tube. Because X-ray tubes are powered by alternating current (AC), the voltage is not constant, and therefore **kVp** is the highest "peak" voltage.

X-Ray Tube Evolution

- X-rays were first produced in the late 1800s and were quickly utilized to treat cancer.
- Gradually, these devices improved by better target systems and cooling the anode with either oil or water, often using a rotating anode.
- In the 1930s–1940s, there were **orthovoltage** units that could deliver energies between 200 and 500 kV, which can treat to a useful depth of around 4–6 cm (Table 3.1).

Cobalt-60 Radiotherapy

- Teletherapy
  - Historically, external beam radiotherapy was delivered by X-ray tubes, which deposited most of the dose to the skin.

Table 3.1 Nomenclature of photon energy ranges: diagnostic X-rays typically in the energy range of 20–150 kV in order to maximize photoelectric effect (see Chap. 4)

X-ray name	Energy	Treatment depth	Uses	Modern utilization
Diagnostic	20–150 kV	–	Imaging	Imaging
Superficial	50–200 kV	0–5 mm	Skin	Rarely
Orthovoltage	200–500 kV	4–6 cm	Skin, ribs	Rarely
Megavoltage	1–25 MV	1–30 cm	Deep tissues	Common

Superficial X-rays closely overlap the diagnostic range and historically were used for superficial skin conditions. Orthovoltage X-rays typically range from 200 to 500 kV and are still used today for skin conditions due to their shallow penetration and narrow penumbra compared to similarly targeted electrons. Megavoltage photons are typically what is used for modern radiotherapy. It is now possible to create extremely high photon energies; however, 18 MV is usually the upper limit of what is used practically due to neutron contamination and an enlarging penumbra with increasing energy.

Dose measured in "skin erythema dose units" – the amount of radiation to make the skin very red or necrose.
Not able to reach deep tissues.
- Cobalt-60 (^{60}Co) discovered with the development of nuclear reactors.
Not found naturally on earth but present in supernovas.
60Co undergoes beta decay to become activated 60Ni, which becomes stable after giving off two gamma rays with energies of 1.17 and 1.33 MeV.
With an average energy of 1.25 MeV, deep tissues are able to be treated with sparing of the skin.
- 1951 – first cobalt teletherapy unit began to be used for external beam cancer treatment.
Largely replaced by linear accelerators (see below) in first-world countries.
Still used today in third world countries where electrical power is expensive or unreliable.

- Gamma Knife
  - Invented shortly after cobalt teletherapy developed.
  - Multiple cobalt sources (usually 201 sources) with holes (apertures) that direct focused radiation to a spherical isocenter.
    The size of the isocenter sphere can be changed by changing the size of the apertures, but the position of the isocenter can only be changed by moving the head to different positions within the helmet.
  - Still used today to treat intracranial lesions.

Linear Accelerators (Linacs)

- Cobalt machines had demonstrated the treatment benefits of megavoltage photons, which allowed better penetration into the body with sparing of the skin.
- The concept of wave guides and the linear accelerator was first thought of in the 1920s (by either a Swedish guy or a Hungarian American depending on whose side you are on).
- These were not used for medical purposes until after World War II when the Varian brothers developed the microwave technology for radio frequency–based particle acceleration.

Operational Theory of Wave Guides

- Electrons are created using an electron gun.
  - This is a cathode–anode system using electrons created by thermionic emissions from a hot tungsten filament, similar to an X-ray tube, except the anode guides the electrons into an accelerator tube (or the Klystron for producing microwaves).
- A wave guide then uses microwaves to accelerate the electrons to just under the speed of light.

  - It is the accelerator tube that allows the production of very high-energy photons and electrons.
  - Traveling wave guides – the beginning and end of the wave are not fixed and so the electrons are **surfing on microwaves**.
  - Standing wave guides – there is a wave and a reflected wave that produce a standing wave (imagine oscillating a slinky or a phone cord connected to the wall). These are expensive to produce but allow a more physically compact system and are what is used most of the time these days.
- It is worth noting that there is a strong magnetic field guiding the wave-guide structure to ensure the electrons move in a straight line with a diameter of about 2 mm (Fig. 3.3).

Bending Magnet Systems

- The waveguide structure pretty much moves in a straight line but that makes positioning logistically difficult. Fortunately, electrons can have their path bent by magnets to whatever direction is desired since they are charged particles. These magnets are usually located in the head of the Linac and bend the electrons

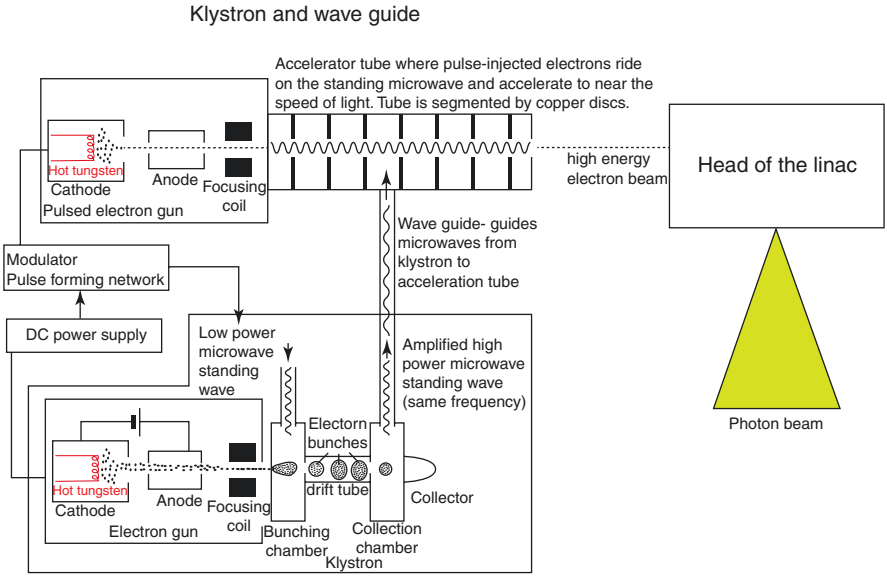

Fig. 3.3 Klystron, wave guide, and accelerator tube: two different electron guns are working at the same time. The klystron uses electrons and a property called bunching to magnify low-intensity microwaves into very high-intensity microwaves (acts as an amplifier). These microwaves are then transported to the accelerator tube where pulsed electrons from a second electron gun ride on microwaves to be accelerated close to the speed of light. The end result is a narrow electron beam, which can then be manipulated into treatment electron beams or photon beams through the head of the linear accelerator

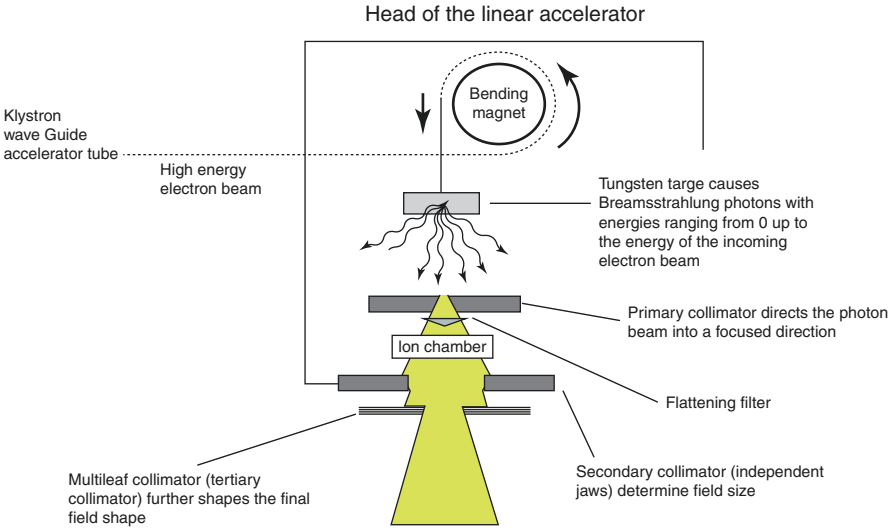

Fig. 3.4 Head of a linear accelerator in photon mode: incoming electron beam from the linear accelerator body is bent 270° around a bending magnet (not all machines use 270° bending magnet) and strikes a tungsten target. The primary collimator directs the beam into the flattening filter. The ion chamber is then able to provide a feedback to reveal the amount of radiation that is actually being emitted for the given amount of power provided. The beam is then shaped by secondary and tertiary collimators into the final size and shape for treatment

270° so that there is a divergence and then a convergence of an electron pencil beam. This also allows electrons that are not the desired energy to crash into the walls in the process of bending around the magnet (see Fig. 3.4).

Flattening Filters (Photon Mode)

- When a photon beam passes out of the primary collimator, it tends to be very intense at the center and fades out around the periphery (sort of like an old-fashioned flashlight beam). The flattening filter makes the beam have a relatively constant intensity throughout.
  - Please note that this is calibrated to the isocenter (100 cm), and therefore, the beam may still be uneven at different depths.
  - Some applications such as stereotactic body radiation therapy (SBRT) prefer treatment without a flattening filter so that the beam is purposely more intense in the center.

Scattering Foils (Electron Mode)

- The scattering foil works similar to the flattening filter by taking the pencil beam of electrons and scattering them over a wide area. Think of what happens when you spray a water hose through a screen door.

Electron Cones (Applicators)

- When functioning in electron mode, there tends to be a significant amount of lateral scatter and divergence due to electromagnetic forces (negative electrons repel each other), even after exiting the secondary collimators. The electron cones shape the beam into the final size and are usually positioned only a few centimeters from the target.

Targets

- Most targets in linear accelerators are made of tungsten due to its **high atomic number** (**Z = 74**) and its **high melting point** (**3422 °C**). High atomic numbers are more likely to produce bremsstrahlung photons, but a lead target would likely melt in an electron pencil beam so tungsten is a good compromise.
- The process of bremsstrahlung radiation is more efficient than in X-ray tubes due to the higher energy, but still about 90% of the energy is lost to heat.

Monitor Chamber

- Immediately after the primary collimator and flattening filter is the monitor chamber. This allows you to know about how much radiation you are delivering.
- The relationship between **monitor units** (**MU**) and dose is complicated and is explored in Chaps. 8, 9, and 10.

Collimation Systems

- Primary and secondary collimators: the primary collimator basically works to point the beam in the forward direction, while the secondary collimator works to define the field size.
- Collimator jaws:
  - Part of **secondary collimator**. A solid block that may be moved in a symmetric or asymmetric fashion.
  - If one jaw is closed to midline and the other is wide open, this is called a half-beam block.
  - Moving the collimator jaw with the beam on can create a dose gradient called a “nonphysical” or “soft” wedge. For details on wedging, see Chap. 9.
- Multileaf collimators (MLC):
  - May be part of **secondary collimator** or may be a tertiary add-on.
  - An array of tiny leaves that can be moved in and out of the beam path to create a variety of shapes.
  - There is more leakage through MLCs than through a collimator jaw, so you want the jaws to come as close as possible to the boundaries of your MLC.
  - For more details on MLCs, see Chap. 8.

- Other collimation systems
  - **Cerrobend**
    Prior to the development of MLCs, radiation beams were shaped by pouring physical blocks in the shape of your target out of liquid metal (cerrobend – a mix of bismuth, cadmium, and lead, an alloy with a melting point of 70 °C).
    Intensity of a beam may be shaped by making some parts thicker and some parts thinner (called a compensator).
  - **Apertures**
    Small holes that allow radiation through with a specific shape (usually a circle) and size.
    Some apertures change size using an iris mechanism.
    Often used in stereotactic systems.
  - **Wedges**
    Made of metal (often steel).
    There are multiple gradients of wedges that can be inserted into the head, which can give a wedged profile to the beam.
    These have been largely replaced by soft-wedges (see Chap. 9).
- Light fields (including field size definition)
  - A light is present within the head of the linear accelerator that will shine through the collimators to give shape of the field.
  - This may be used as a general guideline for treatment setup but remember that field size is defined at isocenter, so unless the patient's skin is at the isocenter, the actual size of the field will be different.

Microtron (Fig. 3.5)

- Basically a linear accelerator where the accelerated electrons travel in a circle and reenter the accelerator to go even faster (or gain mass as they approach the speed of light).
- The loop is controlled by a magnetic field and with each pass of the electron as it gains energy, the loop becomes larger.
- The electrons are eventually captured by a collector tube at the desired energy with the associated radius of the loop.
- This concept can produce electrons of very high energy (up to 1500 MeV).
- Another form of microtron is called a racetrack microtron that uses straight courses with bending magnets on the ends to swing the beam in a "racetrack shape" (see Fig. 3.5).
- This is similar to the synchrotron or cyclotron discussed below except that the circles are generated through an accelerator structure and not generated by electromagnets.
- The microtron was invented around the same time as the linear accelerator and used clinically in the 1970s, but for all practical purposes, a regular linear accelerator is much simpler and is more widely used.

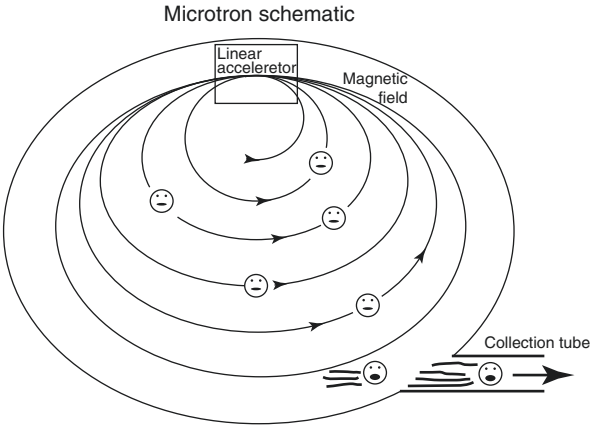

Fig. 3.5 Microtron: the electrons are injected into the linear accelerator and are bent around in a loop by a magnetic field. Each time the electrons enter the accelerator, they gain speed until they approach the speed of light, at which point they begin to gain mass relativistically. They are eventually ejected through a collection tube

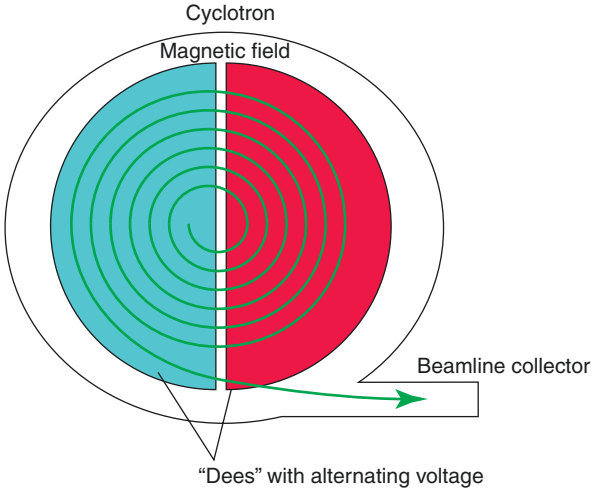

Fig. 3.6 Cyclotron: alternating "dees" or D-shaped electrodes alternate voltage at a specific frequency within a magnetic field to accelerate particles in a circle. With each pass, the circle grows wider as the particle gains energy until it is eventually collected

Cyclotron (Fig. 3.6)

- A cyclotron uses D-shaped electrodes ("dees") that accept alternating voltage in the setting of a static perpendicular magnetic field.
- The frequency of the alternating polarity must match the target particle's "cyclotron resonance frequency" and thus you get a particle that develops a spiral-shaped path, gaining speed and relativistic mass with each revolution until it either crashes into the wall or is collected in the beam tube.
- This allows acceleration of any charged particle for radiation therapy; they are primarily used to accelerate protons.

Synchrotron (Fig. 3.6)

- While the cyclotron uses a constant guiding magnetic field that alternates at a constant frequency, a synchrotron has a variable frequency guiding magnetic field that adapts to the changing mass of particles at every segment as they approach the speed of light.
- Instead of two Ds in a disc, a synchrotron actually looks more like a long thin toroid with magnetic segments that eventually feeds into a storage ring with the useful beam line coming out at a tangent from an outer storage ring.
- One could almost think of it like multiple linear accelerators arranged in a spiral, getting faster and faster as you moved outward. The difference is that instead of linear accelerators, they are electromagnets pulsing on and off at frequencies that are slightly different as the particles move through.
- As the spiral moves wider and the magnets become more powerful, the particles can attain extremely high energies (giga-electron volt range).
- This is how large particle colliders such as the Large Hadron Collider at CERN operate and that is why they are often several miles wide and utilize superconducting magnets.
- In radiation oncology, this is another available method for accelerating protons and heavy ions.

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Interactions of Electromagnetic Radiation with Matter

4

Introduction

Photons are a type of boson that carries electromagnetic energy. They have no charge and are therefore an indirectly ionizing particle. At lower energies, they predominantly interact with matter through coherent scatter and the photoelectric effect. For the photoelectric effect, a photon goes in and an electron comes out. At energies in the range of radiotherapy treatment, the predominant interaction is Compton scatter, where photons bounce off of electrons and transfer some of their energy to the electrons in the process. At higher energies, pair production becomes possible such that a photon will cause the production of an electron and a positron that can cause annihilation. Also at higher energies, photons may interact with the nucleus and cause it to release nucleons. Pair production and photonuclear disintegration are generally undesirable for the purposes of radiation therapy.

How Do Photons Interact?

- This section is all about interactions of photons with matter.
  - While "matter" is generic, in biological tissue it is usually water.
- Since photons have no charge, they are **indirectly ionizing**.
  - This is in contrast to charged particles such as electrons and protons, which are **directly ionizing** (Fig. 4.1).

Definitions

- **Electromagnetic radiation**: Photons. They have both electrical and magnetic properties and are not deflected by either electrical or magnetic fields.
- **Absorption**: Loss of photons from a beam due to photon energy being absorbed by matter.

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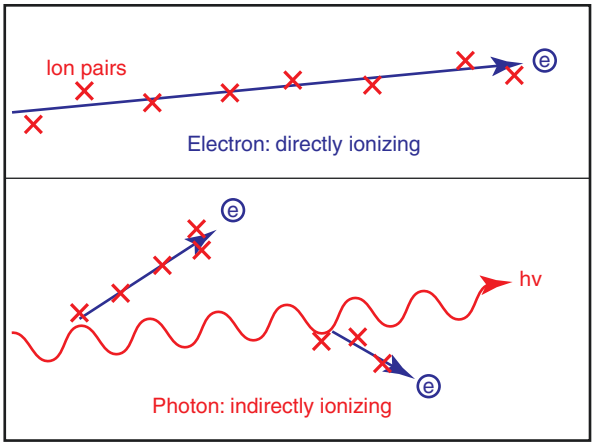

Fig. 4.1 Directly versus indirectly ionizing radiation. Charged particles directly ionize other atoms in the medium by exerting coulombic forces to budge electrons directly off of atoms (see Chap. 5). Indirectly ionizing radiation is not charged and largely relies on secondary electrons (or protons in the case of neutrons crossing biological material) to cause the actual ionizations

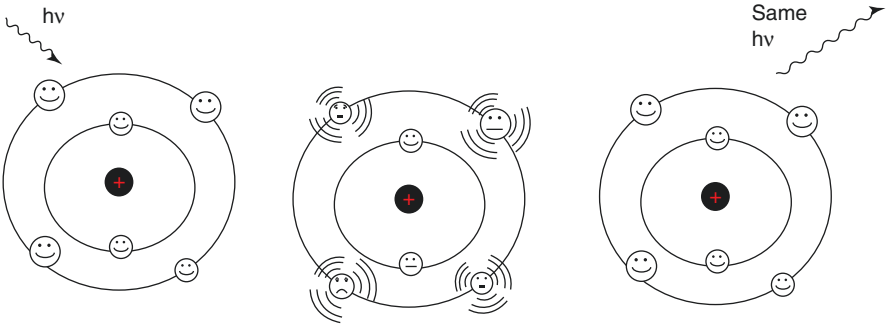

Fig. 4.2 Coherent scatter: the incoming photon is very low energy and is absorbed by the electron orbitals (not enough energy to kick an electron out of the atom), and it causes an excited state (the electrons become very angry). Finally, the electrons settle down and release all that negative energy in the form of another photon with the same energy as the one that caused all the excitement in the first place. The net effect is that a photon bounces off of the atom

- **Scatter**: Loss of photons from a beam due to photons changing direction.
- **Attenuation**: Loss of photons from **absorption** and **scatter**.
  - Please refer to Chap. 7 for more detail.
- **E**: Photon energy
- **Z**: Atomic number

Coherent Scatter (aka Rayleigh Scatter)

- **Occurs at energies of**: **1 keV–1 MeV.**
- **Dominant interaction at**: **<10 KeV** (Fig. 4.2).
- **Photons bounce off of electrons** – it is actually more complicated but think of it that way.

  - Actually, a photon is absorbed by the electrons of an atom, and they begin oscillating at a high frequency.
  - When they settle down, the energy is released as another photon with the same energy as the old one.
  - No net energy is absorbed.
  - The only effect is that a photon changes direction.
  - This does NOT cause ionization; no dose is deposited.
- **Probability of interaction** is **directly proportional to Z**.
  - Happens more in **lead** (**Z = 82**) than **water** (**Z = 1** and **8**), but not overwhelmingly so.

Photoelectric Effect

- **Occurs at energies of**: **1–150 keV.**
- **Dominant interaction at**: **10–26 keV** (Fig. 4.3).
- Photon interacts with an atom and causes it to eject an electron or an X-ray.
  - A photon with energy similar to (but no lower than) the binding energy of an electron will kick out that electron.
  - With a nice new comfortable position available, a less comfortable electron will take its place.
  - This process is similar to internal conversion decay (Chap. 2) except with the energy coming from a photon instead of the nucleus.
  - It either causes **characteristic X-ray** or **Auger electron** emission (see Chap. 1).

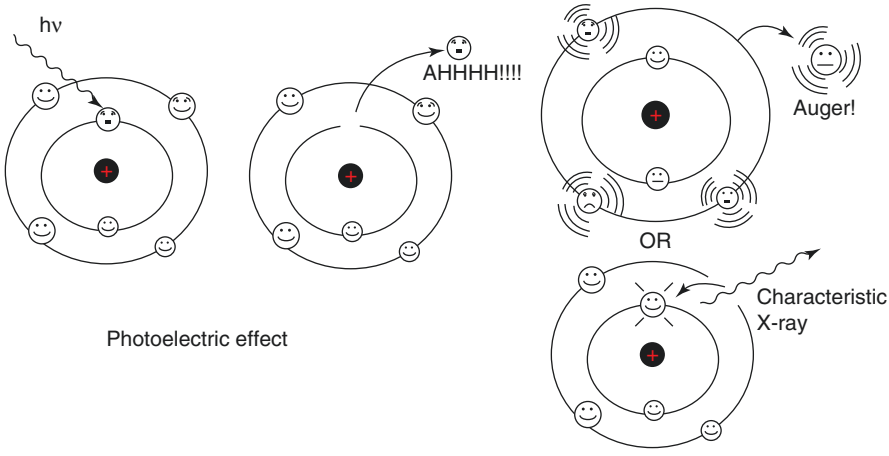

Fig. 4.3 Photoelectric effect: an incoming photon with energy greater than the binding energy of an inner electron knocks it completely out of the atom. The nice comfortable open spot means that a higher energy electrons want to fill it and will therefore shed the extra energy in the form of an Auger electron or a characteristic X-ray (see Chap. 1)

- **Probability of interaction** is proportional to $\mathbf{Z^3/E^3}$:
  - $\mathbf{Z^3}$ (Atomic number cubed): happens WAAAY more in **lead** (**Z = 82**) than **water** (**Z = 1** and **8** for H and O respectively).
  - $\mathbf{1/E^3}$ (inverse energy cubed): happens A LOT at low energy and not at all with higher energies.
- **Photoelectric effect** causes ionization! This effectively breaks molecular bonds causing all kinds of damage!
- **Photoelectric effect** is the most important interaction for diagnostic imaging because of the $\mathbf{Z^3}$ dependence:
  - Bone absorbs a LOT MORE X-rays than soft tissue, showing up clearly on film.

Compton Scatter

- **Occurs at energies of**: **any.**
- **Dominant interaction at**: **26 keV–24 MeV** (Fig. 4.4).
- **Photon is a cue ball in a game of pool** (electrons are the other balls).
  - The photon literally hits an electron and it flies out of orbit with the photon being deflected as well.
  - The electron can go straight forward or any angle up to 90°, like an angle shot.
  - The wider the deflection angle, the slower it will go (same as in pool).
- The photon (cue ball) gets bounced too:
  - At glancing angles, the photon barely changes direction or energy.
  - At 90° deflection, energy is **0.511 MeV** (resting energy of electron).
  - If it is a direct hit on the electron, the photon bounces back 180°; energy is **0.255 MeV** (half of 0.511).

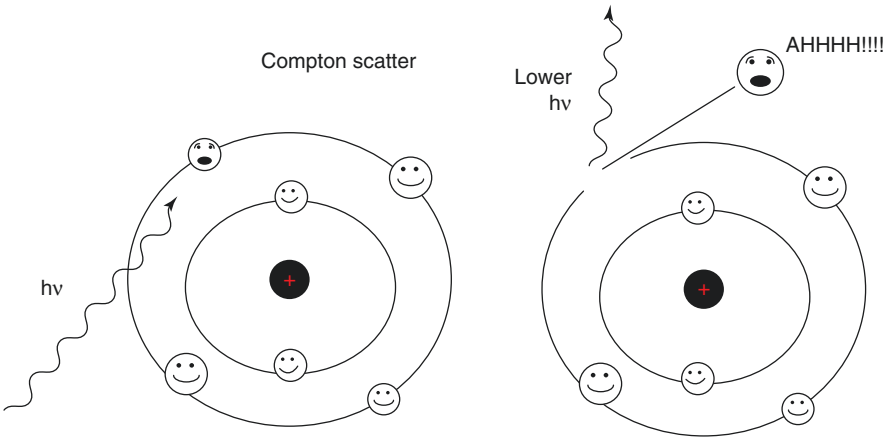

Fig. 4.4 Compton scatter: an incoming photon hits an electron and knocks it out of the atom like a cue ball hitting another pool ball. Part of the energy is transferred to the electron (which is then free to do damage by direct ionization), and the electron's new energy (plus the binding energy of the electron) is lost by the photon

- **Probability of interaction** is proportional to **electron density**:
  - This is roughly proportional to **mass density** for most materials. Therefore, one gram of water is similar to one gram of fat or bone.
  - This is **independent of Z** and therefore less sensitive to bone, lead, and other higher Z materials.
  - This makes Compton effect **most useful** for delivering a uniform dose in radiotherapy.
  - It is bad at producing a sharp image of bone and tissue.

Pair Production

- **Occurs at energies of**: **1.02 MeV and above.**
- **Dominant interaction at**: **10 MeV and above** (Fig. 4.5).
- **Photon is a firework** – a photon with at least 1.02 MeV (usually much more) interacts with the electric field of an atomic nucleus and explodes into an electron and a positron (evil antielectron in figure).
  - The pair moves generally forward and splits the energy in excess of the 1.02 MeV needed to create them (this is the resting energy of the positron and electron by $E = MC^2$).
  - The electron goes off to do whatever it wants but the positron bounces around until it slows down enough to meet another electron and then annihilates the electron (and itself in the process), sending off two photons in opposite directions, each with 0.511 MeV (these can go wreak their own havoc).
- **Probability of interaction** is proportional to $\mathbf{Z^2}$ and **dramatically increases with E**.
  - While small amounts of pair production occur at lower energies, it is really only significant above 6–10 MeV.

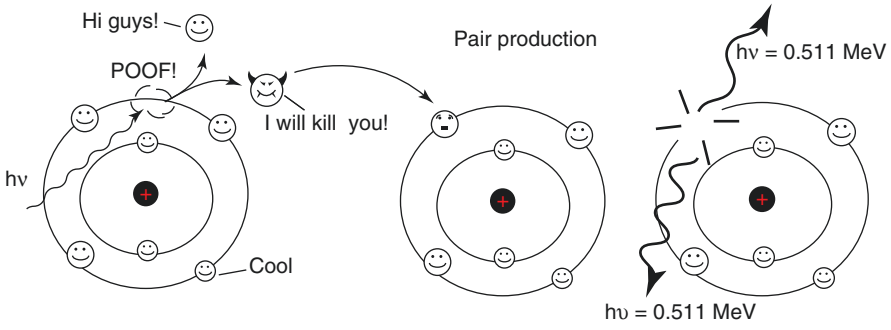

Fig. 4.5 Pair production: A photon is traveling with so much energy that when it hits the electric field of the electron orbitals, it explodes into an electron and an evil positron. The electron wanders off and exerts coulombic forces. The evil positron not only causes ionizations by coulombic forces, but it eventually slows down and finds an electron somewhere else and annihilates it! The resulting mutual annihilation sends two photons in opposite directions with an exact energy of 0.511 MeV

- Pair production adds scatter radiation outside the field, thanks to the positron and annihilation photons.
- This is generally undesirable in radiotherapy if you want tight margins between tumor and protected tissue.
- This is irrelevant for imaging due to the very high energies required.

Triplet Production

- Similar to pair production, but the photon interacts with the electric field of an orbital electron (in an atom).
- The orbital electron is ejected, as well as the electron and positron created out of thin air! (vacuum, really).
- Probability is **proportional to Z**, and the threshold energy is **2.044 MeV** (twice as much as pair production).
- Not a large contributor to radiotherapy dose.

Photonuclear Disintegration

- **Photon is a jackhammer** – at energies above about 8–16 MeV, a photon can actually smash into the nucleus of high-Z atoms and chip off neutrons or even larger chunks (Fig. 4.6).
- When operating a Linac **above 10 MV**, the higher energy photons can interact with the metal components of the head of the machine and send neutrons flying into the patient.
  - This is generally a BAD thing as neutrons have much greater late toxicity than photons.
- Not a large contributor to total dose but is the main source of neutron contamination.

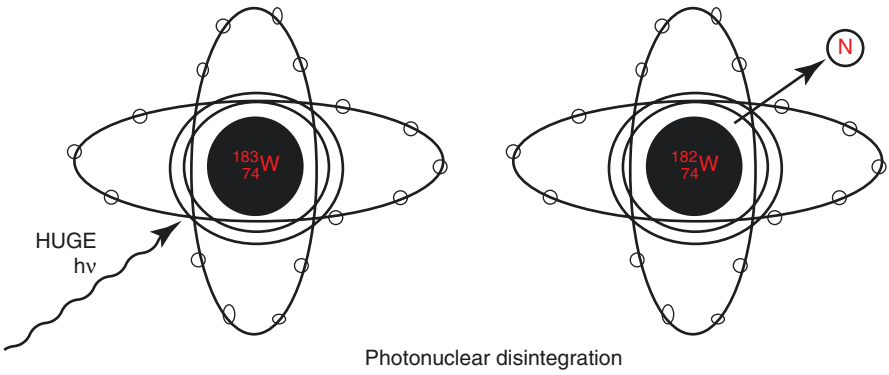

Fig. 4.6 Photonuclear disintegration: a photon hits a nucleus with so much force that it actually knocks a chunk of the nucleus out of the atom (usually neutrons)

Interactions of Particulate Radiation with Matter

5

Introduction

Particle radiation includes electrons, protons, neutrons, heavy nuclei (including alpha particles), and mesons but does NOT include photons for the purpose of describing particle radiotherapy. Particles can be described as charged or uncharged and heavy or light. Charged particles are usually directly ionizing by acting through coulombic forces while uncharged particles are indirectly ionizing, often causing ionization as a secondary consequence of other reactions. Unlike photons, particles have specific distances to travel (ranges and path lengths). The release of excessive energy produces a Bragg Peak when a heavy charged particle comes to the end of its path length. There are specific interactions for particles that define the radiation dose and distribution. Clinical application of proton beam is discuused more in detail in Chap. 18 of this book.

Definition of Range

- Particulate radiation has a finite **range** which is approximately how far they can travel in a medium before stopping.
- For our purposes, whenever we say range, we mean R_{CSDA}, a range defined by the continuous slowing down approximation (CSDA).

Types of Particulate Radiation

- **Charged and uncharged particles**
  - Charged particles can directly interact with electrons and nuclei, through coulombic interactions. Therefore they are "**directly ionizing**" and are generally less penetrating than uncharged particles.

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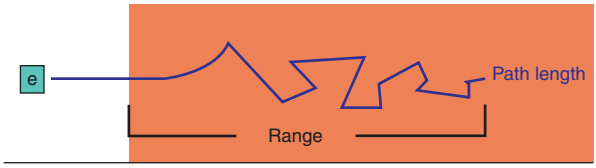

Fig. 5.1 Path length versus range: electrons usually have a tortuous path; thus, path length is always greater than range

  - Uncharged particles cannot interact through coulombic forces, so they are **indirectly ionizing**. Heavy uncharged particles are more likely to interact with nuclei than with electrons, and they are relatively more penetrating.
- **Light and heavy particles**
  - "**Light**" particles are particles with a mass similar to electrons (basically just electrons, positrons, and beta particles).
  - Due to their mass, they change directions (scatter) very easily.
    Path length is much longer than range (Fig. 5.1).
  - "**Heavy**" particles are significantly heavier than electrons, basically everything else. For example, a proton has ~1836× the mass of an electron.
  - Due to their mass, they travel relatively in a nearly straight line.
    Path length is roughly equal to range.

How Do Charged Particles Interact?

- Unlike photons, charged particles are **directly ionizing**.
- Charged particles have a **variable velocity**, unlike photons which always move at the speed of light.
  - **Velocity** and **energy** are directly related to each other; when a particle gains energy, it moves faster.
- Particles gradually lose energy as they interact with the medium.
  - This is in contrast to photons which undergo **attenuation**: decreasing the number of photons in the beam, without changing the energy of the individual photons (Fig. 5.2).
- **Two basic types of collisions**:
  - **Elastic collisions**: think of a game of pool.
    Kinetic energy and momentum are both conserved; energy is transferred between the particle and the medium.
    All of the energy is kept in the form of motion.
  - **Inelastic collisions**: think of a bullet going through a wall.
    Kinetic energy and momentum are not conserved; the particle transfers energy to the medium and slows down.
    This energy may be released as a photon, or it may be transferred to an electron (causing ionization).

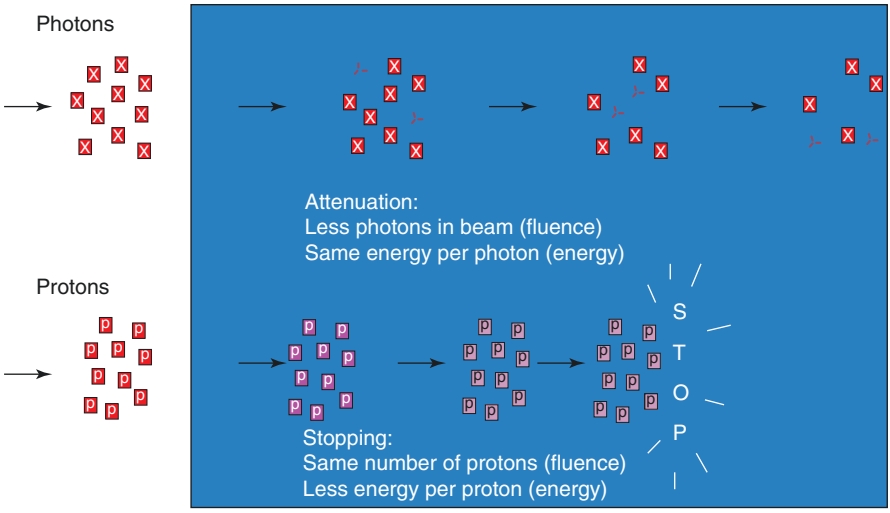

Fig. 5.2 Attenuation versus stopping power: indirectly, ionizing particles (photons) will undergo multiple scatterings and collisions in a random fashion that will decrease the number of photons (fluence – see Chap. 6). Protons and other particles will have paths that decrease in energy as they interact with more atoms through coulombic force but gradually they will slow down and eventually come to a stop with some degree of certainty for a given starting energy. Think of stopping power as the amount of power it takes to stop Mr. Particle (see Fig. 5.3)

Charged Particle Specifications

- The **W value** is the average energy needed to produce an ion pair in a gas.
  - For example, in dry air at standard temperature and pressure, **W** is approximately **33.97 eV**.
  - **W** is very small compared to the typical energy of charged particles (a few MeV for electrons, hundreds of MeV for heavier particles). Each particle makes a lot of ions!
- **Specific ionization** is the number of ion pairs produced per unit path length.
  - **Specific ionization** is higher at low energies and lower at high energies.
  - This is because a high-energy particle moves too fast to have time to interact with surrounding materials.
- **Linear energy transfer** (**LET**) and **stopping power** are closely related concepts that measure the energy transfer between a charged particle and the medium.
  - **Stopping power** is the amount of energy the particle loses per unit path length; think of it as the amount of "drag" on the particle.
  - **LET** is the amount of energy that the particle deposits in local ionizations per unit path length. Think of it as the amount of damage a particle leaves in its track. LET is microscopic quantity used in biology for celluar damage.
- **Specific ionization**, **stopping power**, and **LET** all increase as a particle slows down. This is because it has more time to interact with the medium (Fig. 5.3).

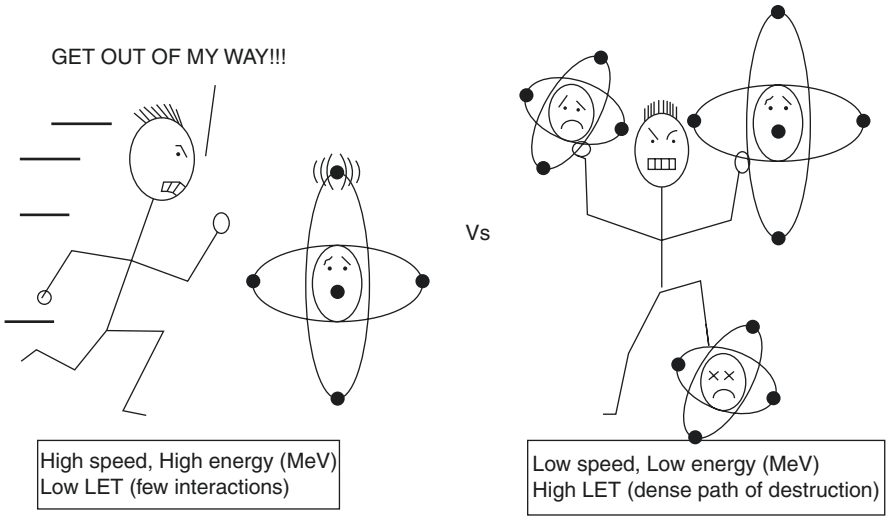

Fig. 5.3 Particle energy and LET: Mr. Particle is a mean dude, but if he is traveling too fast, he can really only throw passing insults at electrons. If he slows down or even stops, all hell breaks loose!

Linear Energy Transfer Relationships

- **LET** is a measure of the interaction between a particle and a medium. See details in Chap. 18.
- **LET increases** with the particle's **charge** (**Q**):
  - **Approximately proportional to Q^2**.
  - **Example**: a 10 MeV **carbon ion** (Q = +6) has a LET of **200 keV/μm**, while a 10 MeV **proton** (Q = +1) has a LET of **4 keV/μm**.
- **LET decreases** with the particle's **velocity** (**V**):
  - **Approximately inversely proportional to V^2**.
  - At energies much lower than the particle's rest mass (mc^2), V^2 is proportional to **Energy** (**E**).
  - At higher energies, **V** approaches the speed of light (**c**) and cannot increase any further.
  - **Example**: a **2 MeV proton** has a LET of **16 keV/μm**, a **10 MeV proton** has a LET of **4 keV/μm**, and a **200 MeV proton** has a LET of **0.4 keV/μm**.
- **LET increases** with the medium's density (**ρ**):
  - **Approximately proportional to ρ**.
  - A particle encounters much more atoms when passing through lead as opposed to air.
- **LET decreases** with the medium's atomic number (**Z**):
  - Even though there are more atoms to beat up in a block of lead, those atoms are a lot tougher to beat up.
  - This can be seen as a screening effect. In a high-Z medium, the large number of electrons around each nucleus cancels out or "screens" some of the nuclear charge.
  - Hence, **Pb** has lower **LET per unit mass** than water.

Stopping Power and Dose

- Stopping power includes two components:
  - **Collisional stopping power** ($\mathbf{S_c}$) – Energy lost due to collisions with the medium. This directly contributes to **dose**, as the energy is deposited locally.
  - **Radiative stopping power** ($\mathbf{S_r}$) – Energy lost to radiative processes such as Bremsstrahlung (see Chap. 3). It does not usually contribute to **dose**, as this energy is radiated away.

Electron Interactions

- **Inelastic collision with atomic electron**:
  - The incident electron transfers some of its energy to an atomic electron, which remains bound (excitation, not ionization).
  - The atomic electron will eventually release this energy as a characteristic X-ray.
  - The target electron remains bound: there is a loss of kinetic energy.
- **Elastic collision with atomic electron**:
  - The incident electron transfers some of its energy to an atomic electron, ejecting it from the atom (**direct ionization**).
  - Kinetic energy is conserved; it is now split between two electrons.
  - The secondary electron may produce additional ionizations (Fig. 5.4).

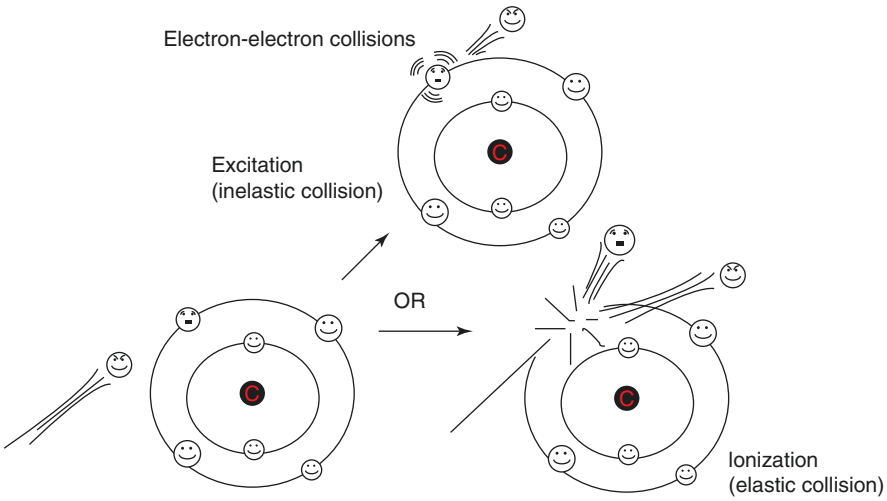

Fig. 5.4 Electron–electron collisions: Mr. Electron mostly interacts with other electrons. He can pass by and raise the energy of an electron orbital, which makes the orbital electron very angry and more inclined to break chemical bonds. When he does this, he slows down a little and loses some of his kinetic energy in the process of making the orbital electron angry; therefore, this is considered an inelastic collision. Alternatively, he can actually hit an orbital electron with enough force to knock him completely out of the atom with an elastic collision where almost no kinetic energy is lost

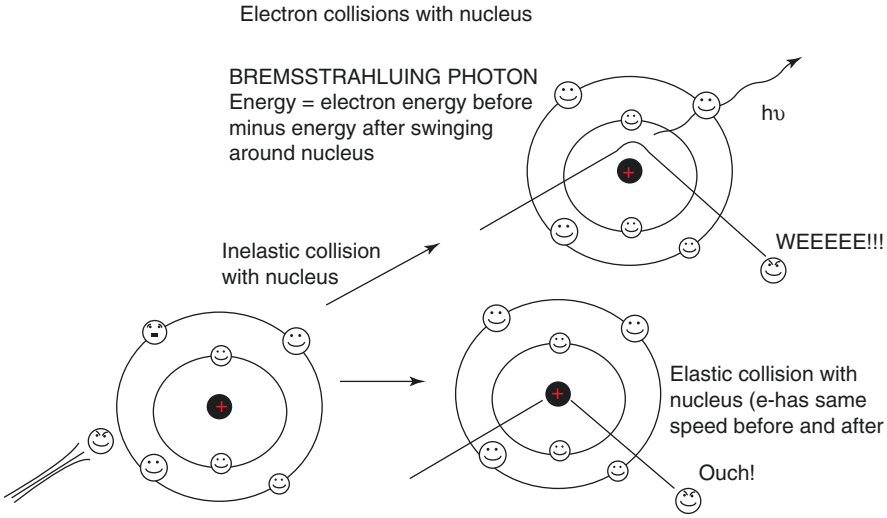

Fig. 5.5 Electron collisions with the nucleus: electrons cannot do a lot of damage to the nucleus but running close to the nucleus can change the path of the electron. If the electron swings around the nucleus without actually hitting it, the electron will slow down and lose some of the energy as a bremsstrahlung x-ray. This is considered an inelastic collision because some of the kinetic energy is lost to the photon. Alternatively, the electron can bounce directly off of an atom with an elastic collision and no kinetic energy is lost; the electron is simply moving in a different direction

- **Inelastic collision with nucleus** (**Bremsstrahlung**):
  - When an electron interacts with the nucleus, it slows down and changes direction.
  - This loss of energy causes a photon to be emitted. The photon is called a **bremsstrahlung X-ray** and is responsible for the production of X-rays in X-ray tubes and linacs.
- **Elastic collision with nucleus**:
  - Since the electron is so much lighter than the nucleus, it does not really transfer energy to the nucleus.
  - Therefore, it merely bounces off (scatters), changing direction without transferring energy (Fig. 5.5).
- **Electron scatter and dose shape**
  - Because electrons scatter so easily, if you look at billions of electrons in an electron beam, each one will follow a unique path through the medium.
  - This is responsible for many of the characteristics of electron beam shapes in the clinic.
  - See Chap. 10 for more details on electron beam dosimetry.

Heavy Charged Particle Interactions

- These principles are the same for protons and "heavy ions" (alpha particles, carbon ions, neon ions, and other heavy things).
- **Inelastic collision with electrons**:

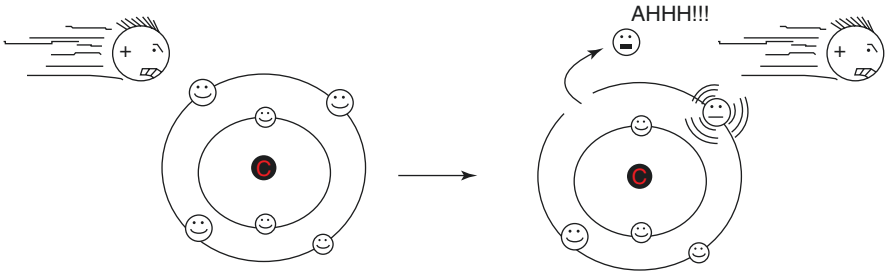

Fig. 5.6 Heavy charged particle inelastic collisions: Mr. Proton is speeding by an electron orbital and sucks an electron right off of its orbital, causing ionization. Every time he does this, he slows down a little and ultimately creates havoc

  - As a heavy charged particle speeds through a medium, its positive charge attracts **thousands of orbiting electrons**.
  - Some electrons are merely excited; others are **ionized**.
  - Each interaction slows the charged particle a little. As it slows, it is more likely to interact with both electrons and the nucleus.
  - The charged particle is very heavy, so it does not change direction appreciably (Fig. 5.6).
- **Nuclear interactions**:
  - Once the charged particle slows to around **0.01 MeV** or so, it is able to interact with the nucleus.
  - Heavy charged particles can experience **Bremsstrahlung** but they have so much mass that this effect is minimal.
  - Interactions between a charged particle and the nucleus can result in various nuclear reactions (see Chap. 2), causing some secondary particles and residual radioactivity.
- **Depth dose characteristics** (**Bragg peak**):
  - As a charged particle is slowed by interactions with the medium, it interacts more and more (**higher LET**) until it finally stops.
  - The burst of energy released around the stop point is known as the **Bragg peak** (Fig. 5.7).

Neutron Interactions

- Since neutrons have no charge, they are not slowed down by electrons. Therefore, they predominantly interact with atomic nuclei.
- Speed (energy) is a major factor for how they interact:
  - **Thermal** (**slow**) **neutrons** have an energy of around 0.025 eV, the approximate thermal energy of room temperature.
  - **Fast neutrons** have a much higher energy in the keV–MeV range.

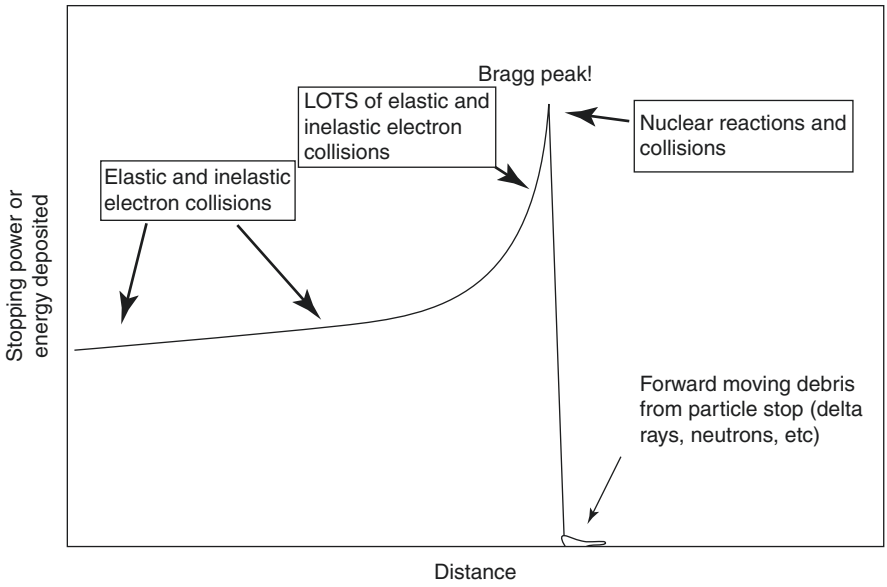

Fig. 5.7 Energy deposition of a charged particle: as a charged particle moves through the medium, it slows down more and has time to do more damage until it comes to a stop and does mega-damage. Even after the final peak of rage, there is a small amount of secondary damage from the debris that was caused at the Bragg peak

Fast Neutron Interactions

- **Elastic collisions with hydrogen nuclei (protons)**
  - Since the neutron has roughly the same mass as a proton, this is the most efficient way for it to transfer kinetic energy.
  - The neutron effectively acts like a cue ball with hydrogen atoms.
  - Neutrons are much less likely to interact with heavier nuclei. Therefore, lead is very poor at blocking neutrons, while water and plastics work well because they contain lots of hydrogen.
  - **This is the predominant interaction for fast neutrons**.
  - This results in a **recoil proton**, which can deposit an additional radiation dose (see **charged particles** section shown in Fig. 5.8).
- **Inelastic scatter**
  - Sometimes a neutron will bounce off of a nucleus and lose energy by emitting a gamma ray (Fig. 5.9).
- **Nuclear spallation**
  - At energies above **7 MeV**, the neutron can undergo an inelastic collision with so much energy that it breaks up the target nucleus.
    This is called **spallation** and the resulting nuclear fragments are called **spallation products**.
  - The spallation products are heavy charged particles, usually alpha particles, and they cause dense ionization nearby (Fig. 5.10).

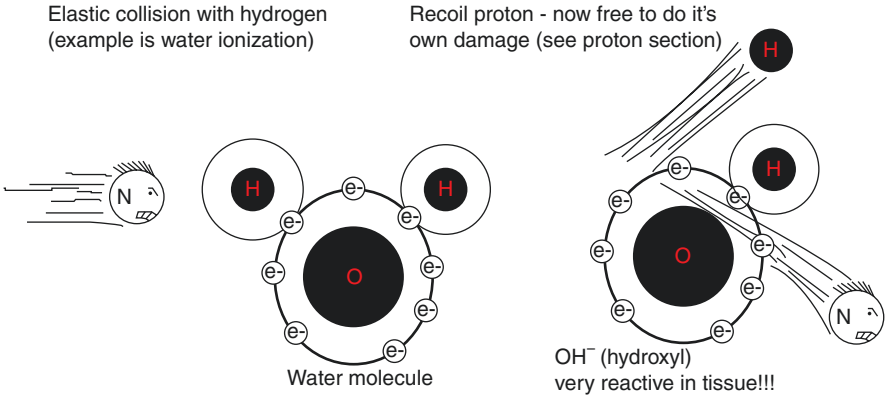

Fig. 5.8 Neutron elastic collisions: neutrons can knock hydrogens right out of their chemical bonds, similar to the way electrons knock other electrons out of orbit

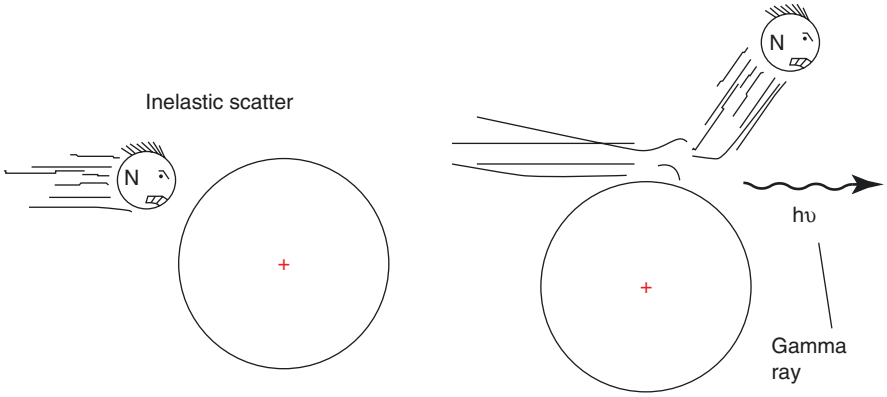

Fig. 5.9 Neutron inelastic collisions: neutrons can bounce off of heavier nuclei and will emit a gamma ray as they slow down and lose energy. This is similar in concept to bremsstrahlung x-rays

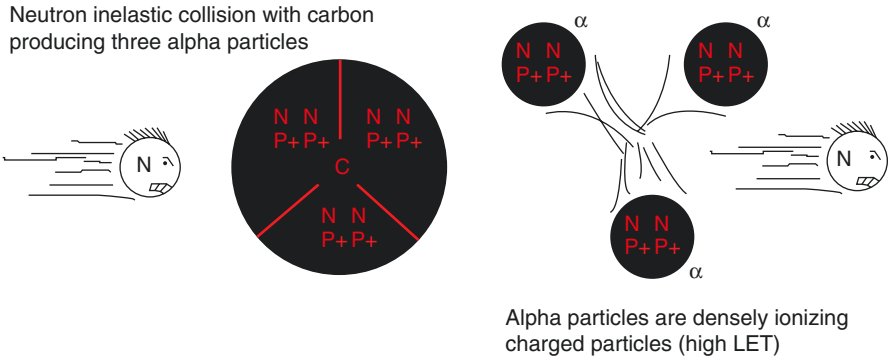

Fig. 5.10 Neutron inelastic collision with spallation: fast neutrons that directly hit a larger nucleus can actually split the atom. This is called spallation and the spallation products (other heavy charged particles) can produce heavy secondary damage to the surrounding atoms

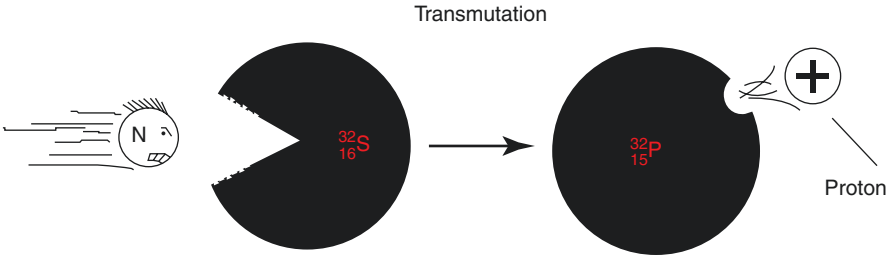

Fig. 5.11 Transmutation: slow neutrons can actually be absorbed into a nucleus and interact with the internal nuclear forces such that the atom ejects a proton or larger particle and becomes a completely different atom (with different chemical properties)

Slow Neutron Interactions

- Once a neutron is sufficiently slow, it can participate in nuclear reactions!
- **Radiative capture**
  - The nucleus absorbs the neutron, gaining 1 AMU but not undergoing any further transformations.
- **Transmutation**
  - The nucleus absorbs the neutron and ejects a proton or alpha particle.
  - This changes the atomic number and therefore completely changes the chemical properties of the atom!
  - When this happens to an atom that is part of a molecule, it will break chemical bonds and disrupt the molecule (Fig. 5.11).
- **Fission**
  - This occurs when slow neutrons encounter a fissile substance such as uranium or plutonium (see Chap. 2).
  - It is not relevant to the medical field, except for nuclear accidents and/or terrorism.

Pions

- **Bonus particle**! As of 2014, nobody uses these for therapy anymore, but who knows, they may come back eventually.
- A Pi-meson or **pion** is a subatomic particle made up of a quark–antiquark pair, as opposed to protons and neutrons, which contain three quarks.
  - Roughly 273× electron mass: still considered a "heavy particle" although much lighter than a proton.
  - Can be negative, neutral, or positively charged.
  - Negative pions can be "fairly easily" produced by smashing a beryllium target with 400–800 MeV protons (the average cyclotron used for proton radiotherapy goes no higher than 250 MeV).

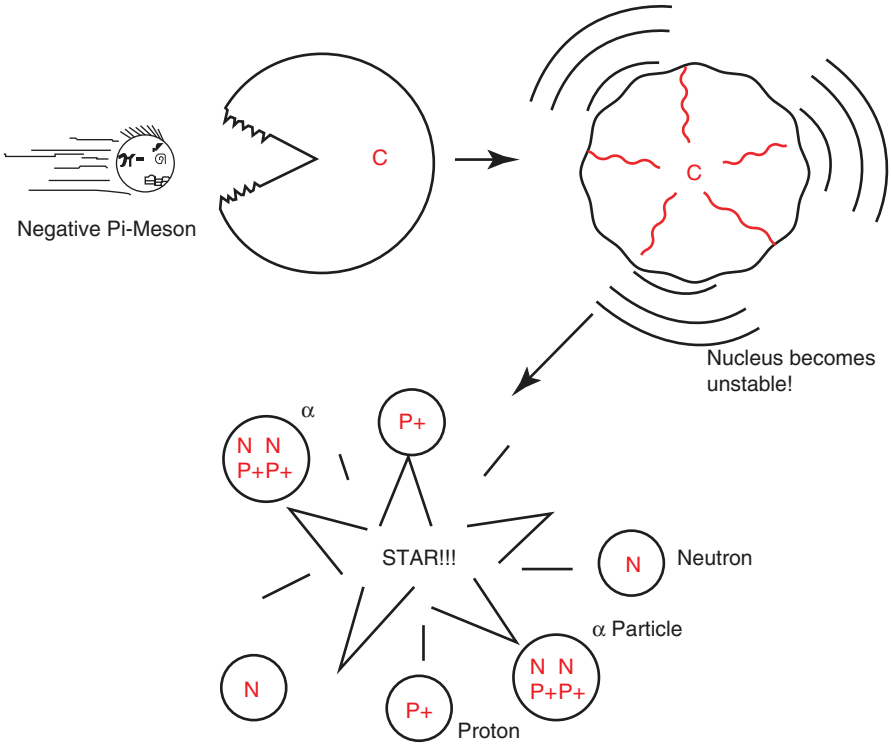

Fig. 5.12 Star formation: a slow-moving negative pi-meson can be absorbed by a nucleus and cause it to become unstable and explode with many charged particles (all of which may damage nearby atoms)

- **Initially**, the negative pion interacts **much like a proton**:
  - It gradually slows down, depositing more and more dose as it slows, with a dose distribution similar to a proton.
- When the Pion comes to a stop (at the **Bragg peak**), it is attracted into a nucleus. Once inside, the nucleus becomes very unstable and explodes into a "**Star Formation**" composed of protons, neutrons, alpha particles, and other nuclear fragments.
  - These fragments deposit a very large amount of energy near the Bragg peak (Fig. 5.12).

Ionization and Biological Action

- Charged particles (electrons, protons, heavy ions, and pions) are considered "**directly ionizing**" because they can directly interact with the electrons around an atom.

- This is in contrast to uncharged particles (neutrons and photons), which cannot directly interact with electrons and create ionization through secondary particles. This is "**indirectly ionizing.**"
- The biological mechanism of radiation damage in living cells is **DNA damage**.
- Ionizations may damage DNA in one of two ways:
  - **Direct action** is direct ionization of the DNA itself and is not oxygen-dependent.
  - **Indirect action** is ionization of water, creating hydroxyl radicals that can react with and damage DNA. This damage is greatly amplified by oxygen.
- **Indirect action dominates at low LET**:
  - Photons, electrons, and fast protons are considered low-LET radiation. Their biological effect is highly oxygen-dependent.
- **Direct action dominates at high LET**:
  - Alpha particles and carbon ions are considered high-LET radiation. Their biological effect is oxygen-independent.
- Do not confuse **directly ionizing** with **direct action**!
  - A 6 MeV electron beam is **directly ionizing** but its biological effect is mainly **indirect**.
- See Chap. 24 for more details on LET and oxygen effect.

Check for updates

Quantification and Measurement of Dose

6

Introduction

Radiation dosimetry is based on exposure defined as C/kg (Roentgen). The energy transferred by photons to a medium is called KERMA, and the subsequent absorption of energy in a medium is quantified as dose, measured in Gray. Due to the different effects of radiation in different tissues as well as the need for radiation safety and protection standards, dose is expressed in Sieverts for equivalent radiation dose and effective radiation dose. Radiation measurements are performed by various types of detectors.

Definitions

- **Gy**: Gray: SI-derived unit of **absorbed dose** in Joules per kilogram.
  - 1 Gy = 100 rads
  - 10^{-6} = micro-(μGy)
  - 10^{-3} = milli-(mGy)
  - 10^{-2} = centi-(cGy) = 1 rad
- **Sv**: Sievert: SI-derived unit of **equivalent radiation dose** and **effective radiation dose** (also in Joules per kilogram).
  - Equal to Gy multiplied by weighting factors for biological effectiveness. Used for radiation safety regulatory limits.
  - 1 Sv = 100 rem (older unit of equivalent/effective dose).
  - 10^{-6} = micro-(μSv)
  - 10^{-3} = milli-(mSv)
- **R**: Roentgen: older unit of measurement for air KERMA or exposure
  - 10^{-3} = mill-(mR)
  - 1 R = 2.58×10^{-4} Coulombs per Kilogram

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- C/kg is the SI unit for air KERMA or exposure – there is no eponym presently.
- dmax: the depth where the maximum dose is deposited (usually given in centimeters).
- Dmax: the maximum dose as a percentage of the prescription dose (describes the magnitude of a hot spot).

KERMA and Dose

- **KERM**A – **K**inetic **E**nergy **R**eleased in **M**edia (the A was added to prevent it from being a dirty word in German apparently). Technically, it is defined as:

$$K = \frac{dE_{tr}}{dm} \tag{6.1}$$

- $\mathbf{E_{tr}}$ is the sum of the initial transferred kinetic energies of all charged particles set in motion by photons in mass (**m**).
- In other words, **KERMA** is the energy **transferred to the secondary electrons from the primary photons**. It is NOT the same as the absorbed dose but it has the same basic units of measurement (J/kg) (Fig. 6.1).

Equation Terms

- **Linear attenuation coefficient** (**μ**):
  - The fraction of how many photons are removed per unit path-length either from scattering out or from transferring their energy to electrons.
  - Measured in $\mathbf{cm^{-1}}$.
  - Dependence:

    Electron density: heavier atoms like calcium in bone get more photoelectric effect and pair production.

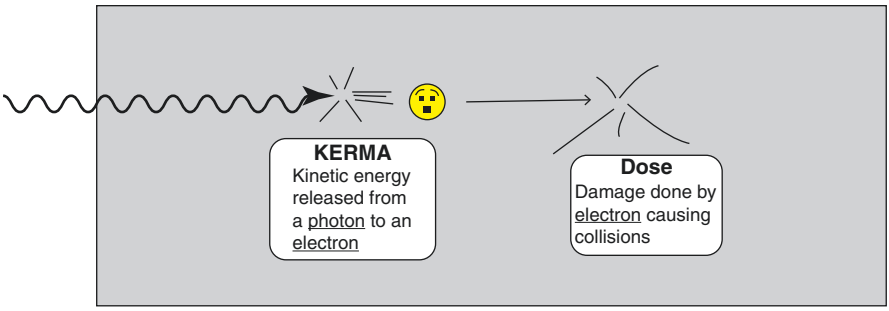


Fig. 6.1 KERMA versus dose: KERMA is the kinetic energy transferred from the photon to the electron. Dose is the energy deposited to the medium in the form of ionizations and excitations

Physical density (**ρ**): muscle attenuates more than lung even though both tissues are mostly water by mass.

– By dividing **μ** over **ρ**, you get the "average **mass energy transfer coefficient**" with units of Kg^{-1} denoted below:

$$\left(\frac{\bar{\mu}_{tr}}{\rho}\right)$$

- **Energy fluence** (**E**ϕ) **or flux** (**Ψ**) is the total energy per unit area (**a**) of a beam, as follows:

$$\Psi = E \times \phi = E \frac{n\ (\text{number of particles})}{a\ (\text{area in cm}^2)} \tag{6.2}$$

KERMA Equations

- Since we now have energy fluence over a beam cross section (**Ψ**) and energy lost per unity mass in a linear fashion, we can combine the mass energy transfer coefficient, Eqs. 6.1 and 6.2, into the following equation:

$$K = \Psi \times \left(\frac{\bar{\mu}_{tr}}{\rho}\right) \tag{6.3}$$

- Even though the energy initially comes from photons, it is the electrons set in motion by the photons that do the final damage (or dose). Most of the energy from the electrons (at least for our purposes) can be considered **collisional KERMA** ($\mathbf{K_c}$).
- Some of the electrons will bend their path, especially if there is metal or other high Z material nearby and create bremsstrahlung photons, which then escape the medium and contribute nothing to the absorbed dose. This is called **radiative KERMA** ($\mathbf{K_r}$).

$$K = K_c + K_r \tag{6.4}$$

- Only K_c contributes to absorbed dose and we do not really care about K_r because it is a small number that translates to a correctional factor. Since we are only interested in K_c, we can rearrange Eq. 6.3 to describe what we are looking at when we turn a beam on:

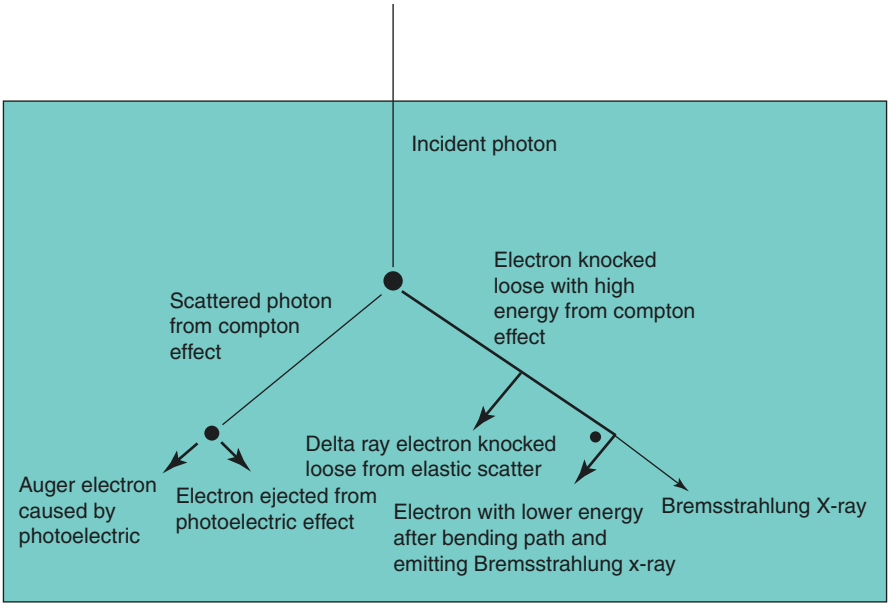


Fig. 6.2 History of an incident photon: in this figure, the path length of photons is thin lines, while the path of electrons is heavy lines. In this example, four different electrons and a Bremsstrahlung X-ray are set into motion by a single initial photon. KERMA is the sum of the kinetic energies of these electrons set into motion by the initial photon. All of these secondary electrons will go on to produce ionizations and excitations. The energy deposited by these secondary electrons is dose and the energy deposition will tend to occur deeper than the KERMA transfer

$$K_c = \Psi\left(\frac{\bar{\mu}_{tr}}{\rho}\right)\times\left(1-\bar{g}\right) \tag{6.5}$$

- Where **g** is the fraction of energy lost to bremsstrahlung photons (it is a substitution for what would have been the K_r term) (Fig. 6.2).

KERMA → Dose

- Photons cause a cascade of electrons (through KERMA) but the electrons do the real ionizing damage (deliver the "dose").
- Since the most important interaction is Compton scatter, which generally propels electrons forward, it makes sense that the most damage done by electrons will not be directly at the surface but will actually be slightly deeper.
- The depth of greatest damage or "maximal absorbed dose" is $\mathbf{d}_{\mathbf{max}}$. The energy transfer from photons and the dose of energy absorbed are related.
- In the buildup region, KERMA is greater than the dose. The dose and KERMA curves eventually cross and then descend on a relatively straight linear slope where the curves are parallel but the dose is slightly greater than KERMA (Fig. 6.3).

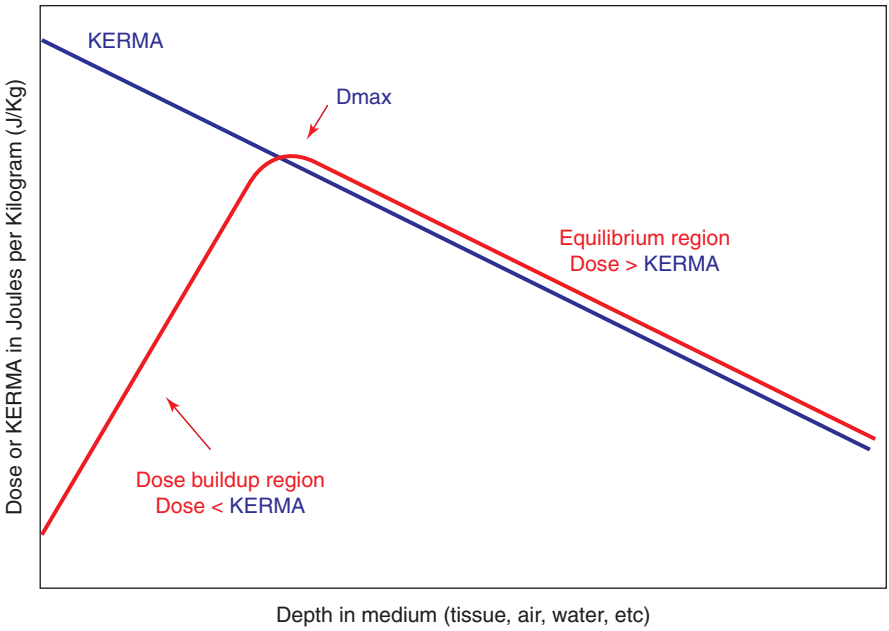
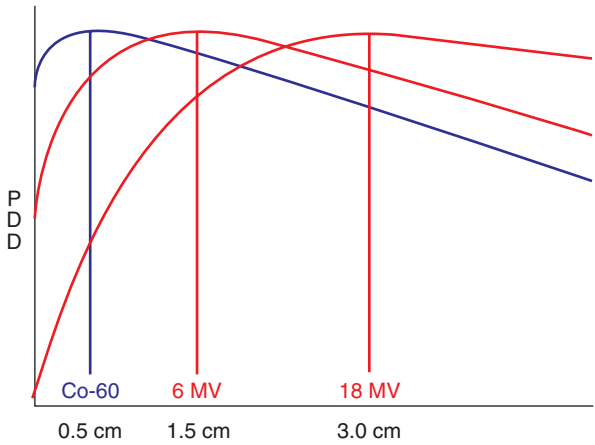


Fig. 6.3 Dose versus KERMA at depth. After equilibrium, dose is always higher than KERMA

Fig. 6.4 Percent depth dose of various photon energy spectrums with an extended view of the x-axis



- The amount of dose buildup from KERMA is based on the photon energy.
  - As photon energy increases, the buildup region also increases and the d_{max} becomes deeper.
  - There is also less dose fall-off with depth (high energies penetrate deeper).
  - In general, we describe doses in percentages, in order to make curves that show the percent of dose at depth (PDD). We will discuss this in much greater detail in the chapter on photon dosimetry (Chap. 9) (Fig. 6.4).

Relative Biologic Effectiveness (RBE) (See Chaps. 21 and 24)

- Not every Joule of radiation energy inflicts the same amount of damage in a complex cell.
- RBE is a unitless number that can be multiplied by physical Gy to calculate a "cobalt Gy equivalent" (CGE). For example, 10 Gy of protons with an RBE of 1.1 could be described as a dose of 11 CGE.
- The main damage responsible for cell killing is a DNA double-strand break (DSB).
  - Radiation that is more likely to break both strands of DNA at the same time is more efficient at killing with the same amount of absorbed dose.
  - If you pack all that energy transfer into one small but powerful explosion and that explosion happens to be very near the DNA double strand, then you are sure to destroy that DNA (alpha particles, carbon ions, etc.).
  - If you stretch that energy into a long strand of energy loss (high-energy photons), then you will produce lots of little single strand breaks and, hopefully, two of them will be close enough to create a double strand break.
    Higher dose per fraction means higher probability of DSBs.
- **Factors that affect RBE**
  - **Linear energy transfer** (**LET**) describes the amount of radiation deposited per unit length. When comparing the same type of radiation with different energies, energy is inversely proportional to LET.
    Heavy particles and slow neutrons typically have high LET.
    High-energy photons typically have low LET.
    Even though all photons have the same relative weighting ratio of 1, lower-energy photons actually have a higher LET than high-energy photons because they deposit more energy in a small space than the high-energy photons.
  - Magnitude of dose per fraction and fractionation schedule (think of the power of stereotactic body radiotherapy when compared to standard fractionation).
  - Dose rate (sometimes cells can repair sublethal damage).
    Most important when considering brachytherapy.
    This has also been brought up for external beam cases where there is a very long setup time between different beams to the same target.
    Very little effect on high LET radiation.
  - Biologic system.
    Inherent repair mechanisms.
    Dividing time of target cells.
    Endpoint desired (or trying to avoid) due to damage.
- Protons have an RBE of about 1.1, although it may be higher at the tip of the Bragg peak.
- Neutrons and heavy particles are much more complex but can have an RBE as high as 40 depending on the energy and the target tissue. This concept will be discussed in much greater detail in the radiation biology sections.

Dose Equivalent (See Chap. 22)

- The **International Commission on Radiation Protection** (**ICRP**) has created weighting factors ($\mathbf{W_R}$) to account for the differences in dose quality for the different types of radiation.
- Used for radiation protection calculations.
- Expressed in Sieverts (Sv) instead of Gray.
- Unlike RBE, which is intended to be a precise measurement of acute cell killing, weighting factors are a conservative estimate of late toxicity used for radiation protection regulations. These numbers may differ, for example, proton therapy beams have an RBE of ~1.1 but a W_R of 2.0.
- Weighting factors according to ICRP report 103:
  - Photons and electrons get a weighting of 1 ($\mathbf{W_R = 1}$).
  - Protons and charged pions get a weighting factor of 2.
  - Alpha particles and other heavy nuclei get a weighting factor of 20 (in other words the energy deposited from 1 Gy of alpha particles is expected to do 20 Gy worth of damage in the tissues, except that it is expressed as 20 Sv).
  - Neutrons vary by velocity (energy).
    1 MeV neutrons get a weighting factor of about 20.
    10–100 MeV or between 0.1 and 0.01 have weighting factors of between 5 and 10.
    >100 or < 0.01 MeV weighting factor is around 2.5.

Exposure

- Exposure (air KERMA) is charge released into a mass of air. Exposure is not the same as dose because it measures the number of ionizations, as opposed to the total energy deposited via ionization.
- The classical unit is the Roentgen, which is often pronounced "renkin" and is denoted by **R**. Thanks to a popular HBO miniseries, you may have heard that 3.6 R/hr is "not great, not terrible."
- While R is no longer used to measure radiation dose to patients, it is still the default unit of measurement for portable survey meters. A meter does not have enough information to calculate dose, but it can measure electrical charge (exposure).
- When photons interact with air, an ion pair is produced, with one positive and one negative charge. If we measure the difference in charge (dQ) divided by air mass (dm), then we can measure "exposure" (X) by the following equation:

$$X = \frac{dQ}{dm} \tag{6.6}$$

- The SI unit is the Coulomb per kilogram (C/kg) and does not have an eponym.

$$1R = 2.58 \times 10^{-4}\,\mathrm{C/kg\ \ air} \tag{6.7}$$

Methods of Measuring Dose

An Explanation of Gas-Filled Detectors

Imagine if you had two large plates with a potential difference (positively and negatively charged such that if you connected the plates, you would get an electrical current, similar to a capacitor). Now imagine that a photon comes between those plates and splits a nitrogen molecule in the air into an electron and a nitrogen ion. The electron would move to the positive end and the nitrogen ion would move to the negative plate. You now have a net charge difference (dQ = differential of charge) that can be measured with an electrometer. Now multiply this concept by about a billion. When you have billions of these reactions, you can measure the amount of photons coming through by looking at the difference in charge (dQ) divided by the mass of air between the plates (dm). This satisfies Eq. 6.6. Some of the ionizations that happen will send electrons outside the plates, but some of the ionizations will also occur in a region outside the plates and send ions into the path of the plates. As long as the rate of ions moving in is the same as those moving out, you have electronic equilibrium. You must attain electronic equilibrium or else you will not be truly measuring air KERMA accurately (Fig. 6.5).

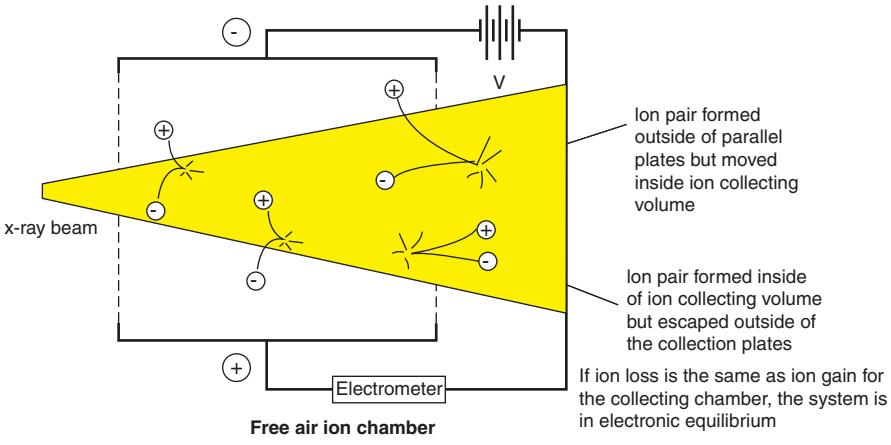


Fig. 6.5 Free air ion chamber and electronic equilibrium: ionizing radiation causes ionizations in air. If a voltage potential is applied between a volume of air, the ions will move toward their respective electrode and the charge can be measured in C/kg. In order to be accurate, ions entering the volume from the outside must be equivalent to ions escaping the volume of measurement, known as electronic equilibrium

- **Calculation of absorbed dose from exposure** (**e.g.**, **f factor**)
  - Under certain circumstances, you can actually determine dose directly from radiation exposure in air (ion chamber). The formula is relatively simple even though it looks complicated:

$$\text{Dose} = \text{Exposure} \times \left(\text{Various conversion factors}\right) \tag{6.8}$$

$$D_{\text{med}} = X \times f_{\text{med}} \times A \tag{6.9}$$

- D_{med} = dose in the medium
- X = exposure – what your instruments will tell you
- A = conversion factor $\left(\Psi_{med}/\Psi_{air}\right)$ or the ratio of energy fluence in the medium to fluence in air
- f_{med} = **roentgen-to-rad factor** – for most things in the body, this is **slightly less than 1** (except for bone at photon energies below about 200 keV where it can be as high as 4.25 due to photoelectric effect).
- **Bragg–Gray cavity theory**: for photons above 3 MeV (Most therapeutic photons in the modern era), exposure cannot be directly measured due to the long range of secondary electrons in air.
  - The Bragg–Gray cavity theory states that if you have a gas-filled chamber (cavity) embedded in a medium, and the cavity is small enough that its existence would not change the number or distribution of electrons that would have been there anyway, then you CAN measure dose based on exposure with the following relationship:

$$D_{\text{med}} = J_g \times \left(\frac{\bar{W}}{e}\right) \times \left(\frac{\bar{S}}{\rho}\right)_g^{\text{med}} \tag{6.10}$$

- D_{med} is the absorbed **dose** in the medium.
- $J_g \times \left(\frac{\bar{W}}{e}\right)$ = energy absorbed per unit mass of the cavity of gas (what you can detect from the small ion chamber embedded in the medium).
- $\left(\frac{\bar{S}}{\rho}\right)_g^{\text{med}}$ is a conversion factor (the ratio of the mass stopping power of the medium to that of the gas for electrons).

- **Ion chambers**
  - The gold standard for radiation measurement is the free air ionization chamber. Unfortunately, this setup requires size requirements proportional to the electron range in air (very large for megavoltage photon beams). Additionally,

since the medium is free air, the setup is very sensitive to changes in temperature, pressure, humidity, and the electrical field. For these reasons, true free air ion chambers usually only exist at national standards laboratories (where you send in your testing gear to be calibrated).

- **Thimble chambers**
  - To make the ion chamber more compact, you can have a central electrode and an outer shell. The number of electrons entering must be the same as those exiting in order to achieve electronic equilibrium, and this would normally require a very large air cavity.
  - This can be overcome however if you make walls around the air cavity that were much more dense than air but had the same atomic numbers as air molecules. With the "dense air equivalent" shell around the air cavity, the chamber can be made small enough to be clinically useful.
  - If it is small enough to be inserted into a material such that the distribution of electrons would not be much different if it were not present, then it meets the Bragg–Gray cavity criteria and can be used to calculate the dose in that region. Exposure for a thimble chamber can be calculated as follows:

$$X = \frac{Q}{\rho \times v} \times \frac{1}{A} \tag{6.11}$$

- X = exposure
- Q = charge measured by the electrometer
- $\rho\, v$ = mass of air (density of air times volume of air)
- A = conversion factor accounting for the fluence difference if the chamber were not present (slightly less than 1.00).

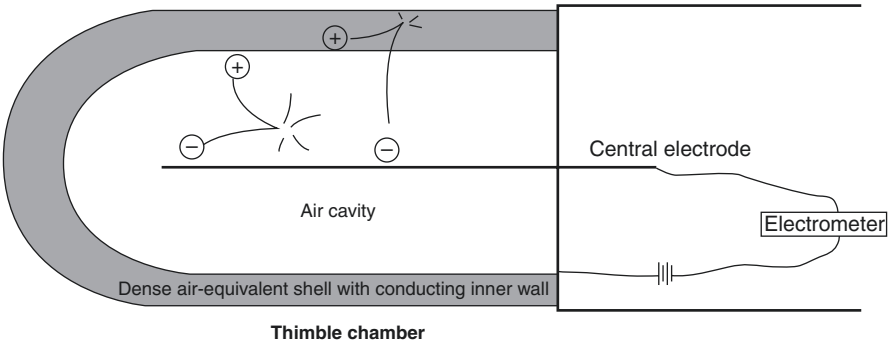


Fig. 6.6 Thimble chamber: instead of parallel plates, a central electrode and a conducting shell can be used to measure charge. The dense air equivalent shell allows the chamber to be significantly reduced in size while still maintaining electronic equilibrium and therefore accurate measurements

  - Because the thimble chamber still uses air, the density of air is still sensitive to ambient pressure and temperature and these must be taken into account and corrected for during measurements (Fig. 6.6).
  - **Condenser chamber**
    It works as a capacitor and measures voltage drop in the presence of radiation with a known conversion factor for voltage drop per roentgen of exposure.
    It is sensitive to photons up to ~2 MeV and insensitive at higher energies due to electrons jumping from the metal stem or the insulator material (called stem effect or stem leakage). These detectors are no longer used in radiation therapy.
- **Farmer chamber**
    Generally, the workhorse of the radiation oncology department, it is a relatively stable and reliable chamber for photons of all energies in the therapeutic range.
    The thimble wall is made of pure graphite and the central electrode is made of aluminum or graphite.
    It has a guard electrode to prevent leakage current from the collector electrode and to define the collecting volume more consistently.

- **AAPM TG-21** – Calibration of a chamber and measuring dose.
  - First protocol – very complicated with many correction factors.
  - **TG-21** has fallen out of use in the modern era as **TG-51** is both simpler and more accurate.

$$D_{\text{med}} = M \times N_{\text{gas}} \times P_{\text{ion}} \times P_{\text{repl}} \times P_{\text{wall}} \times \left(\frac{\bar{L}}{\rho}\right)_{\text{air}}^{\text{med}} \tag{6.12}$$

- D_{med} = dose to the medium (what you want to find out).
- M = charge measured on the electrometer.
- N_{gas} = calibration of gas cavity in terms of absorbed dose to the gas per unit charge or electrometer reading – unique for each ionization chamber.
- P_{ion} = correction factor for ion recombination.
- P_{repl} = correction factor for perturbation of fluence due to the chamber being present.
- P_{wall} = correction factor for the wall of the chamber.
- $\left(\frac{\bar{L}}{\rho}\right)_{\text{air}}^{\text{med}}$ = average restricted mass collisional stopping power of electrons – dependent on energies.
  - The important thing to remember about TG-21 is that it is **dose to a medium based on air KERMA (exposure) measurement calibration** and has many variables that require reference to tables of stopping power ratios and mass energy absorption coefficients.

- **AAPM TG-51** is slightly more accurate but immensely more simple and based on an **absorbed dose-to-water calibration factor**.
  - The equation is as follows:

$$D_w^Q = M \times k_Q \times \mathrm{N}_{D,w}^{60\mathrm{co}} \tag{6.13}$$

  - D_w^Q = dose to water at the reference point in beam quality Q.
  - M = charge measured with the electrometer.
  - k_Q = Quality conversion factor that is specific to each thimble chamber and energy – should be listed on the packaging of your thimble chamber or on a table in the TG-51 protocol. By definition, k_Q = 1.000 for a ^{60}Co beam with any chamber.
  - $N_{D,w}^{60\mathrm{co}}$ = Absorbed dose-to-water calibration factor for ^{60}Co.

- **Thermoluminescent dosimetry** (**TLD**)
  - Basic idea: **cumulative radiation dose is stored in a crystal** that can be read later by heating it.
  - It has been largely replaced by optically stimulated luminescence dosimeters (**OSLD**s) in the modern era.
  - What actually happens is that ionizing radiation causes electrons in a crystal's electron orbitals to jump to a higher state and instead of relaxing to the ground state, they are trapped due to impurities (usually magnesium) in the crystal lattice.
  - Later, they can be heated and cooled, which allows the electrons to fall back to the ground state. When this happens, photons are released, which can be measured. A few downsides include the fact that these crystals can be saturated, and also over a long time, the electrons will escape the traps on their own and therefore give an inaccurate reading. Common crystals include LiF, CaF_2, and $Li_2B_4O_7$. These are typically used in American personal dosimeter badges and rings (most of the rest of the world uses film badges). They can also be used in small spaces.
- **Optically stimulated luminescence dosimeter** (**OSLD**):
  - It rides on the same concept as TLD but instead of heating the material, it can be stimulated with laser to release the trapped electrons. One example material is aluminum oxide doped with carbon and it releases luminescence of 420 nm when illuminated with a stimulation light of 540 nm.
- **Calorimetry**
  - Basic idea: **ionizing radiation heats up water**. You can measure the temperature change in a body of water or graphite and get the dose that was delivered.
    1 Gy = 2.4×10^{-4} °C in water
    Note that this is a really small temperature change!
  - Ionizing radiation can cause excitations or ionizations that eventually lead to electrons moving to higher shells, which leads to molecules vibrating faster, which is basically the concept behind heat. In fact, all (or a large known

fraction) of the absorbed radiation eventually appears as heat and therefore, this can be measured with very high accuracy in theory. This requires special equipment with high precision and is not considered very practical.

- **Film**
  - Basic idea: **radiation exposes a film similar to a camera**
  - **Radiographic Film**:
    A plastic film is covered with silver bromide, and when the film is hit by photons (light or ionizing radiation), a chemical reaction takes place such that when the film is developed, metallic silver is left on the film and the rest is washed off to leave an image. The amount of radiation corresponds with the amount of silver left over and therefore the darkness. Electron beams and megavoltage photon beams can have their isodoses measured relatively accurately but more importantly, the shape of a beam can be determined. Downsides of the film are light contamination, confounding effects of kilovoltage X-rays (photoelectric effect on silver), and film processing inaccuracies.
  - **Radiochromic Film**:
    Uses a different material that is closer to tissue equivalence and produces a colored picture instead of a silver one. Advantages for this type of film include more beam energy independence and insensitivity to visible light (though it is still sensitive to UV light).
- **Chemical dosimetry**
  - Basic idea: radiation causes a chemical reaction. If you can measure the chemicals that reacted, you can measure the radiation that hit the chemistry set.
  - Many systems exist but the only one worth mentioning is "Fricke" dosimetry where irradiated ferrous ions (Fe^{2+}) are oxidized by radiation into ferric ions (Fe^{3+}). The recipe for such a dosimeter is 1 mmol/L ferrous sulfate, 1 mmol/L NaCl, and 0.4 mol/L sulfuric acid.
  - The concentration of ferric ions can then be easily measured by spectrophotometry (UV absorption peaks at 224 and 304 nm). Unfortunately, not all photon energies create the same number of reactions, so there are tables of "G values" which are the number of molecules produced per 100 eV of energy absorbed. The number is about 15.5 molecules per 100 eV absorbed and this G value does not change much for energies used in radiation oncology.
- **Solid-state diodes**
  - Basic idea: silicon chip acting as an ion chamber.
  - A silicon crystal is mixed with different impurities on two sides. One side is the N-type region that is electron-rich. The other side is the P-type region that is full of electron holes (positive region). These almost act as the parallel plate electrodes in the ion chamber.
  - The area between these two regions is the "depletion zone" and this acts like the air cavity in an ion chamber. When ionizations occur from photons, the depletion zone ionizes into electrons and holes.

  - The electrons move to the p-type region and the "holes" move to the n-type region. This creates an electric current that can be measured to extreme precision.
  - The geometry of practical diodes actually resembles a thimble chamber and it is mounted on a coaxial cable. Silicone is about 1800 times more dense than air and the energy required to produce an electron–hole pair is about 1/10 of the energy required to make an ion pair in an ion chamber, so the current produced per unit volume is about 18,000 times that of an ion chamber and therefore they are extremely sensitive.
  - Unfortunately, they have detector positioning variability, energy dependence in photon beams (though not in electron beams), and mild temperature dependence. They also take on damage over time. Their main use is in patient dose monitoring.
- **Metal oxide semiconductor field effect transistors** (**MOSFETs**):
  - Solid-state detector for radiation dosimetry (similar in principle to diodes)
  - Due to small size (0.2×0.2 mm^2 in area and 0.5–1.0 μm thickness of SiO_2), it offers a high degree of spatial resolution and is suitable in small field dosimetry.
  - MOSFET exhibits a linear dose response with ±2% reproducibility.
  - The MOSFET response is independent of dose rate from 100 to 600 MU/min and dose per pulse from 0.2 to 0.5 mGy/pulse for 6 MV photons.
  - Limited lifetime: there is some temperature dependence and some energy and directional dependence due to the Si substrate behind the sensitive volume.
  - A major disadvantage of all MOSFET detectors is their short life, which depends on the maximum accumulated dose before hole-traps become saturated.

    The saturation value of the signal varies with the sensitivity of the MOSFET (expressed as mV/cGy).
- **Scintillation detectors**
  - Basic idea: small amounts of incident radiation generate visible light photons that can be measured precisely.
  - When charged particles strike a scintillator, atoms are excited such that they release photons that can be measured by a photomultiplier tube. This is a precise setup that can measure very tiny amounts of radiation along with information on the intensity and energy of incident radiation. This is sometimes used in radiation survey meters for radiation safety monitoring.

Characteristics of Photon Beams

7

Introduction

Photon beams are characterized by their intensity and energy. The attenuation coefficient measures the rate at which the beam is attenuated (loses intensity) at depth. A half-value layer is a thickness of material that decreases the intensity to half of its original value. In a polyenergetic photon beam, lower energies are attenuated more rapidly than higher energies. Therefore, the average energy of the beam increases with attenuation. This effect is known as filtration or beam hardening. Beam quality is a measure of a photon beam's penetration and can be measured by thickness of a half-value layer in a specified metal, or by percentage depth dose in water.

Definitions

- **Energy** (**E**) measures the amount of energy in each photon.
- **Intensity** (**I**) and **fluence** (ϕ) measure the total number of photons per unit area, **#/cm^2**.
- **Attenuation** measures the decrease in **intensity** (number of photons) as a beam passes through matter.
  - **Attenuation** is a concept specific to photons. Charged particles do not undergo **attenuation**, but rather undergo **slowing** and **stopping**.

Intensity Versus Penetration

- It is easy to get confused between these two concepts. They are very different!
  - **Intensity** (fluence, number of particles) tells you how much dose a beam can give, but not how deep that will go.
  - **Penetration** (energy, beam quality) tells you how deep the beam will go, but not how big that dose will be.

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- When dealing with **filtration** and **beam hardening**, **intensity** and **penetration** are actually inversely related.
  - **Filtration** decreases **intensity** but increases **penetration** by selectively filtering out lower-energy photons in a polyenergetic beam.

Attenuation Coefficients

- **Linear attenuation coefficient** (**μ**) measures the rate at which photons are attenuated per centimeter of material encountered (see Chap. 6 for details).
- **Mass attenuation coefficient** $\left(\mu/\rho\right)$ is the linear attenuation coefficient divided by the density of the attenuating material. This is used for calculations such as "how much mass is needed for shielding?"
- **Partial attenuation coefficients** ($\mu_1, \mu_2, \mu_3, \ldots$) are used to analyze different components of attenuation.
  - For example, "attenuation due to photoelectric effect," "attenuation due to Compton scatter," and "attenuation due to pair production."
- The sum of all partial coefficients should equal to the total (**linear**) **attenuation coefficient**.

Mathematics of Attenuation (Fig. 7.1)

- A narrow beam of monoenergetic photons attenuate in a simple exponential fashion:

$$I(x) = I_0 \times e^{-(\mu x)} \tag{7.1}$$

  - Starting at an initial intensity of $\mathbf{I_0}$, **I** decreases exponentially with **Depth** (**x**).

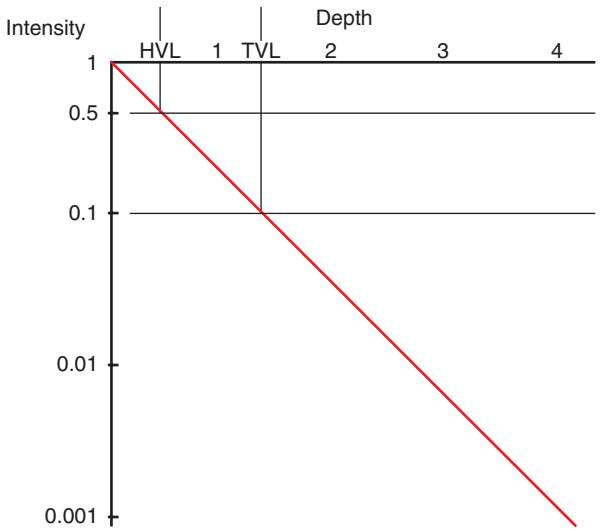

Fig. 7.1 Simple attenuation. Intensity decreases by a factor of 2 with every half-value layer and by a factor of 10 with every tenth-value layer

- This equation should look familiar; it is similar to **Activity** (**A**) versus **Decay Constant** (**λ**) and **Time** (**t**) (see Chap. 2).

$$A(t) = A_0 \times e^{-(\lambda t)} \tag{7.2}$$

- **Attenuation coefficient** relates to **half-value layer** (**HVL**) like **decay constant** relates to **half-life**:

$$\mathrm{HVL} = 0.693 / \mu \tag{7.3}$$

$$I(x) = I_0 \times e^{-(0.693x/\mathrm{HVL})} \tag{7.4}$$

$$I(x) = I_0 \times 2^{-(x/\mathrm{HVL})} \tag{7.5}$$

- A **tenth-value layer** can be defined as 3.32 **half-value layers**, or **2.3/μ**. This is the depth at which the primary beam has one-tenth its original intensity. This is often used for shielding calculations for a radiation facility.

$$\mathrm{TVL} = 2.3 / \mu = 3.3 \times \mathrm{HVL} \tag{7.6}$$

Attenuation Geometry

- What is "**good geometry**" and "**bad geometry**" in the context of attenuation measurements?
- **Narrow beam geometry** is an ideal situation where only the primary beam is measured. This maximizes the accuracy of attenuation measurement and is called **good geometry** (Fig. 7.2).
- The contribution of scatter and secondary radiation can be minimized by:

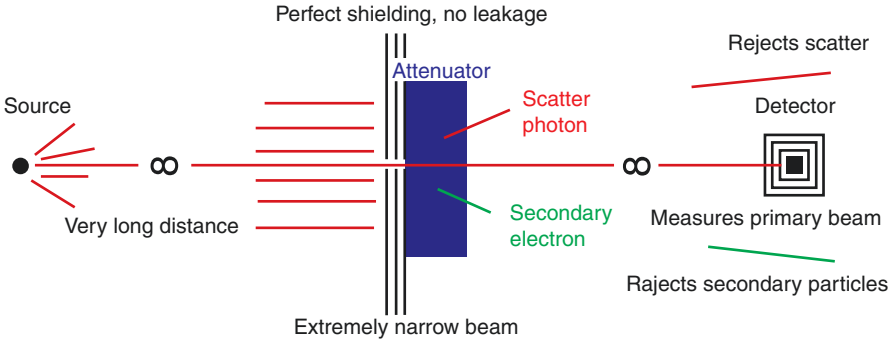

Fig. 7.2 Narrow beam geometry uses a combination of narrow beam and long distance to minimize the amount of scatter and secondary particles that reach the detector

  - Very small field size (narrow beam).
  - Very long source-to-target distance.
  - Very long target-to-detector distance.
- Narrow beam geometry produces the most reproducible **attenuation coefficient** (**μ**) because it does not include field size and scatter effects; both of them are effectively **zero**.
- **Broad beam geometry** allows scatter and secondary radiation to reach a detector.
  - In the context of measuring primary beam attenuation, this is **bad geometry**.
  - Broad beam measurements are useful for calculating **shielding** requirements for a radiation facility (see Chap. 14).

Narrow Beam Versus Broad Beam Attenuation

- A **broad beam** has a smaller attenuation coefficient than a **narrow beam**.
  - Some of the attenuation is "canceled out" by **scatter**; therefore, the coefficient is smaller.
- A **broad beam** has a **thicker HVL** than a **narrow beam**.
  - You need a thicker barrier to shield against a broad beam.
  - This makes sense because you have to shield against both **primary beam** and **scatter** (as opposed to just the primary beam).

Monoenergetic and Polyenergetic (Spectral) Beams

- A **monoenergetic** photon beam has a fixed energy and does not change with attenuation at any depth.
- However, a **polyenergetic** (spectral) photon beam changes in energy as it is attenuated.
  - Low-energy photons attenuate more rapidly than high-energy photons.
  - Thus, the average photon energy will increase as the beam is attenuated (Fig. 7.3).

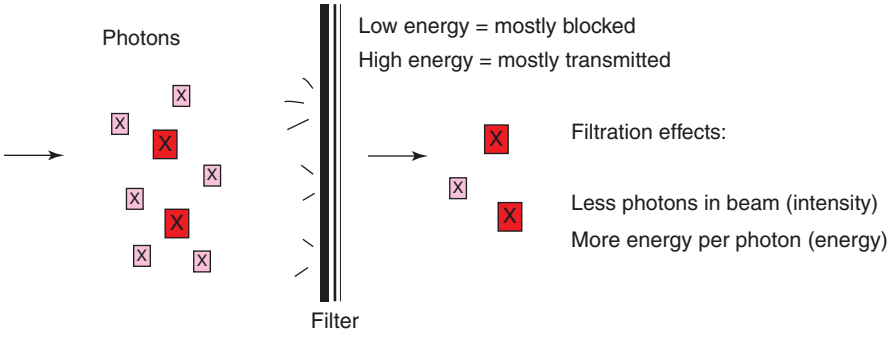

Fig. 7.3 Filtration. Placing a filter in a polyenergetic beam will selectively attenuate the lower-energy photons. This increases the average energy of the beam, but decreases the intensity of the beam

- This phenomenon is known as **beam hardening**, also known as **filtration**.
- Due to **beam hardening**, the second **HVL** is thicker than the first **HVL**, the third is even thicker, and so on.

$$HVL_1 < HVL_2 < HVL_3 \tag{7.7}$$

- Most of **beam hardening** occurs over the first **tenth-value layer** (TVL) (3.3 HVLs).
  - For shielding calculations it is assumed that after the first **TVL**, all subsequent **TVL**s remain the same.

Filtration in Clinical X-Ray Beams

- The **inherent filtration** of an X-ray beam depends on the type of X-ray target:
  - **Reflection targets** have **minimal inherent filtration**, only the glass and oil in the X-ray tube.
    Diagnostic and kilovoltage/orthovoltage X-rays.
  - **Transmission targets** have **high inherent filtration** as the beam passes through the entire target.
    Megavoltage X-rays.
- **Added filtration** comes from any devices placed into the beam:
  - **Uniform filters** are placed in kilovoltage beams to increase the **beam quality** (**effective energy**).
  - **Flattening filters** are placed in megavoltage beams to eliminate the "forward peak." Therefore, they provide more filtration at the center and less at the periphery.
    Because the peripheral beam is less penetrating, it may cause superficial hot spots known as "**horns**" (Fig. 7.4).

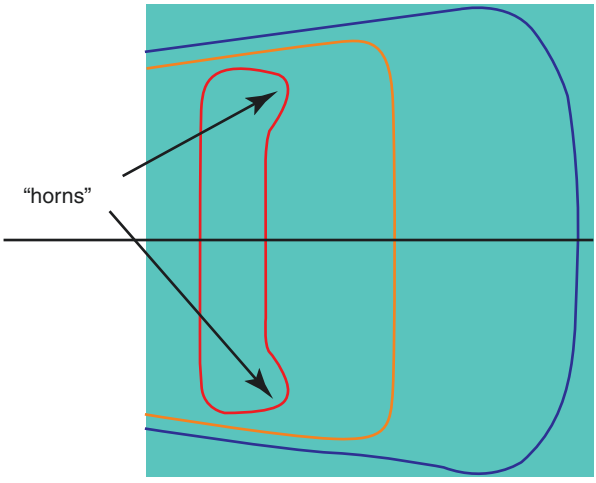

Fig. 7.4 Photon beam horns. In a megavoltage beam, there is much less filtration on the beam edges than in the center. For this reason, the beam edges are hot superficially, but cold at depth

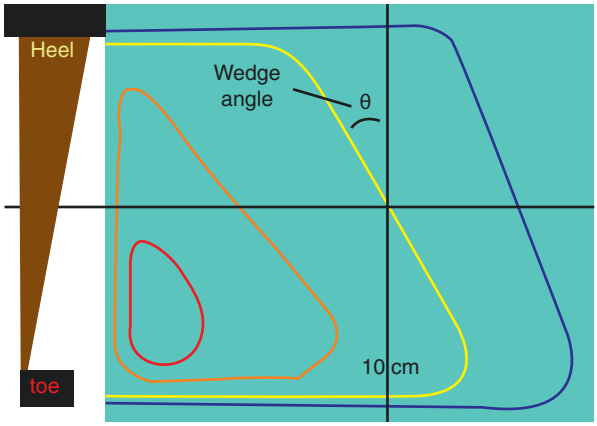

Fig. 7.5 Wedge angle: due to beam hardening, the "heel" of the wedge is more penetrating than the "toe". This causes the isodose lines to become less sharply angled with depth

  - **Physical wedges** result in a less intense but more penetrating beam at the **heel**. This causes the angle of the isodose lines to decrease with depth (Fig. 7.5).
- For kilovoltage X-rays, **filters** are constructed of a series of metals arranged from **high atomic number** (**high-Z**) to **low-Z**. This is done to decrease the production of **characteristic X-rays**.
  - **Example**: A Thoraeus filter is made of **tin** (**Z = 50**), **copper** (**Z = 29**), and **aluminum** (**Z = 13**).
  - **Tin** absorbs part of the primary beam and produces mid-energy characteristic X-rays.
  - **Copper** absorbs the characteristic X-rays from **tin** and produces low-energy characteristic X-rays.
  - **Aluminum** absorbs the characteristic X-rays from **copper** and produces minimal characteristic X-rays because it is very light.
  - The order of these materials is very important. A Thoraeus filter will not function properly if inverted.

Beam Quality

- **X-rays** are produced when **monoenergetic electrons** strike a target, creating **polyenergetic photons** via bremsstrahlung (see Chap. 3).
  - Measuring the exact energy spectrum is difficult and not practical for the clinic.
- **Beam quality** is a description of how penetrating the photon beam is.
  - "**High beam quality**" means highly penetrating and "**low beam quality**" means less penetrating.
  - This does not guarantee a high-quality image or treatment!
- There are many ways to specify **beam quality**.
- **Peak** (**nominal**) **energy** is the most simplistic measure:

  - **50 kVp**, **250 kVp**, **6 MV**, **18 MV**, **and so on**.
  - Two **50 kVp** beams may have very different penetration depending on how much filtration there is.
  - Therefore, peak energy is a very imprecise measure of **beam quality**.
- **Half-value layer** (**HVL**) is used to specify beam quality in the diagnostic (kilovoltage) and orthovoltage range:
  - Specifically, this is $\mathbf{HVL_1}$ measured under **narrow beam** geometry.
  - Peak energy and **HVL** are often combined to specify orthovoltage beam quality.
  - For example, "**250 kVp**, **HVL = 2 mm Cu**" may specify a therapeutic orthovoltage beam.
- Commonly used metals for measuring **HVL**:
  - **Aluminum** (**Al**), **Z = 13**: for 100 kVp unit.
  - **Copper** (**Cu**), **Z = 29**: for 250 kVp unit.
  - **Tin** (**Sn**), **Z = 50**: for 500 kVp.
  - **Lead** (**Pb**), **Z = 82**: for Co-60 and higher.
- **Percentage depth dose** (**PDD**) is used to specify beam quality for megavoltage beams (**TG-51**).
  - This is measured in **water**, at a **10 cm depth**, with a **10 × 10 cm² field size**, and **100 cm SSD**.
  - This is called $\%\mathbf{dd(10)_x}$ in **TG-51** nomenclature for high energy beams >10 MV.
  - Other measures of megavoltage beam quality exist, but $\%\mathbf{dd(10)_x}$ is the most up-to-date standard.
  - For example, "$\%\mathbf{dd(10)_x = 67}\%$" may specify a therapeutic megavoltage beam.

Effective Energy

- **Effective energy** is the energy of a **polyenergetic photon beam** with the same **beam quality** as the beam being measured.
  - The effective energy of **kV** beams is based on **HVL**.
  - The effective energy of **MV** beams is based on **PDD**.
- **Rule of thumb**: the **effective energy** of an **X-ray** beam is approximately one-third **of the peak energy**.
  - For example, a **4 MV X-ray beam** has an approximate **effective energy** of **1.33 MeV**.
  - This is rather similar to **Cobalt-60** (**1.25 MeV**).

Check for updates

Dosimetry of Photon Beams in Water

8

Introduction

The purpose of dose calculations is to determine how many monitor units are required to deliver a desired dose. The formulae and techniques in this chapter provide several methods for calculating monitor units, depending on treatment setup variables such as source-to-surface (skin) distance/source-to-axis distance (SSD/SAD), field size, depth, wedges, and other factors. SSD setups are calculated using percent depth dose (PDD)-based formulae, while SAD setups are calculated using tissue-air ratio/tissue-phantom ratio/tissue-maximum ratio (TAR/TPR/TMR)-based formulae.

Definitions

- **D** = Dose
- **d** = Depth (sometimes called z)
- $\mathbf{D_{max}}$ = Maximum dose to a point, defined as = 100%
- $\mathbf{d_{max}}$ = The depth of $\mathbf{D_{max}}$ (sometimes called $\mathbf{z_{max}}$)
- **SSD** = Source-to-surface (skin) distance
- **SAD** = Source-to-axis distance
- **PDD** = Percent depth dose
- **TAR** = Tissue-air ratio
- **TPR** = Tissue-phantom ratio
- **TMR** = Tissue-maximum ratio
- **SAR** = Scatter-air ratio
- **MU** = Monitor Unit
- **K = Calibration factor (cGy/MU)**
- **OF**, $\mathbf{S_{cp}}$ = Output Factor
- **ISF** = Inverse Square Factor
- $\mathbf{S_c}$ = Collimator scatter

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- $\mathbf{S_p}$ = Phantom scatter
- **WF** = Wedge factor
- **TF** = Tray factor

How Does a Dose Calculation Work?

- What is a **Monitor Unit** (**MU**)?
  - **MU** for linacs is analogous to "beam on time" for Co-60 and orthovoltage units.
  - **MU** is measured by an ion chamber inside a linear accelerator (linac) head.
- Linacs are calibrated so that **1 MU = 1 cGy** under a specific **reference condition**, variable among institutions.
  - Measured in water phantom.
  - **SSD setup** (SSD = 100) versus **SAD setup** (SSD < 100).
  - **10 × 10 cm² field size**, almost always.
  - Reference Depth varies (d_{max}, 5, 10 cm)
- As we change our prescription depth, field size, shape, and so on, we will need more or less beam to deliver the same dose.
  - The purpose of dose calculation is to figure out how much **MU**!

SSD and SAD Setups

- **SSD setup** uses a constant distance between the source and the surface/skin.
  - **SSD** can be changed as needed (100, 110 cm, etc.).
  - Increasing the depth of the prescription point will increase its distance from the source.
  - **PDD** is used for **SSD** dose calculations.
- **SAD setup** uses a constant distance between the source and isocenter.
  - This allows for rotation around a fixed isocenter and is therefore much more common for modern-era radiation therapy.
  - **SAD** is a fixed value for any given machine (80 cm for Co-60, 100 cm for linac).
  - **TAR/TMR/TPR** (collectively known as **TXR**) are used for **SAD** dose calculations.

Hand Calculation (SSD Setup)

$$\text{Dose} = \text{MU} \times K \times \text{ISF} \times \text{PDD} \times S_c \times S_p \times \text{WF} \times \text{TF} \tag{8.1}$$

$$\text{MU} = \frac{\text{Desired_Dose}}{K \times \text{ISF} \times \text{PDD} \times S_c \times S_p \times \text{WF} \times \text{TF}} \tag{8.2}$$

- **What are all of these factors**?
  - **K = Output Factor** (**cGy** per **MU**):
    K = 1.0 if linac was calibrated to d_{max} at 100 SSD.
    Otherwise, it may be different, and may also vary with field size.
  - **ISF** = Inverse square factor:

$$\text{ISF} = \left(\frac{\text{SSD}_{\text{ref}} + d_{\text{max}}}{\text{SSD} + d_{\text{max}}} \right)^2 \tag{8.3}$$

  - $\mathbf{SSD}_{\text{ref}}$ = SSD under reference conditions.
  - **PDD**, $\mathbf{S_c}$, $\mathbf{S_p}$, **WF**, **and TF** are each discussed next.

Percent Depth Dose (PDD)

- **PDD** is defined as a percentage of $\mathbf{D_{max}}$, measured at different depths within a water phantom at a fixed **SSD** (usually 100 cm).
- Due to the fixed **SSD**, the source-to-detector distance will increase with increasing depth.
  - **PDD** changes with depth due to buildup, attenuation, and distance (inverse square factor).
- The shape of the **PDD** curve depends on beam energy:
  - Higher energy beams have a larger buildup region and therefore have a lower **PDD** at low depth ($\mathbf{<d_{max}}$).
  - Higher energy beams are more penetrating and therefore have a higher **PDD** at high depth ($\mathbf{>d_{max}}$).
  - The surface dose, **PDD** (**d = 0**), decreases significantly with beam energy. This is responsible for skin sparing and the build-up effect at superficial depths.
- **PDD** (**10 × 10 cm² field**, **d = 10**) increases with beam energy and is used to measure **beam quality** in **TG-51**.
  - For a detailed discussion of beam quality, see Chap. 7.

Extended SSD

- Does extending the SSD make you hot or cold?
  - **It depends**! What is the question being asked (Fig. 8.1)?
- Radiation is like heat; if you put wings directly on the grill, they will cook much faster than if you put them on the top rack.
  - **Extended SSD** decreases the **inverse square factor** (**ISF**), so it takes more beam-on time (**MU**) to deliver the same dose.
- The wings on direct heat are more likely to burn the skin before cooking the center, while wings on the top rack will cook more evenly.

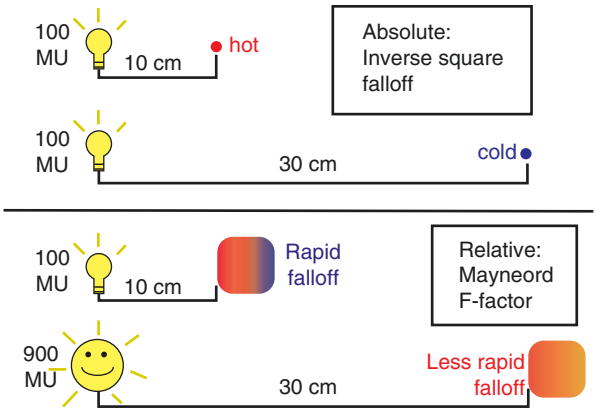


Fig. 8.1 Extended SSD effects. When SSD is extended, dose decreases according to the inverse square law (an absolute decrease). However, dose will no longer fall off as rapidly with depth (a relative increase)

- Dose homogeneity improves with **extended SSD**.
- **10 cm depth** is very deep relative to **20 cm SSD**, but not so deep relative to **200 cm SSD**.
- Therefore, **PDD** increases with **SSD**.
- The magnitude of this increase can be calculated by the **Mayneord F-factor** (named after the British physicist who first described it).

Mayneord F-Factor

- **Mayneord F-factor Mnemonic**:"**Old and deep**" (old SSD + d) * "**new and shallow**" (new SSD + d_{max}), over the opposite, and then squared.

$$\frac{PDD_2}{PDD_1} = \left(\frac{(SSD_1 + d) \times (SSD_2 + d_{max})}{(SSD_2 + d) \times (SSD_1 + d_{max})} \right)^2 \tag{8.4}$$

- The F-factor (the bracket term in Eq. 8.4) is usually a small adjustment. Under normal circumstances it is just a few percent.
  - If you do an F-factor calculation and end up with 1.10 or 1.20, you probably made a mistake. Double-check your numbers.

S_C and S_P: Scatter Factors and Field Size

- Increasing the field size increases the output (**cGy/MU**) – why?
  - **Primary dose** does not change.
  - **Scatter dose** increases with field size.

    Scatter dose is zero for an infinitely narrow beam, because anything that scatters exits the beam.

A broader beam allows more of the scatter to remain inside the field.

- **Scatter factors** are divided into two components:
  - **Collimator scatter** ($\mathbf{S_c}$) comes from the linac head (mostly the primary collimator, not the collimator jaws) (Fig. 8.2).

$$S_c(r) = \frac{\text{Dose in air for field size } r}{\text{Dose in air for reference field } \left(10 \times 10 \text{ cm}^2\right)} \tag{8.5}$$

- Phantom scatter (S_p) comes from the phantom (Fig. 8.3).
  - Measuring dose in a phantom gives a combination of collimator and phantom scatter. Therefore, the collimator scatter must be divided out:

$$S_{c,p}(r) = \frac{\text{Dose in phantom for field size } r}{\text{Dose in phantom for reference field size}} \tag{8.6}$$

$$S_p(r) = \frac{S_{c,p}(r)}{S_c(r)} \tag{8.7}$$

  - When blocks or multileaf collimators (MLCs) are used, the field size for $\mathbf{S_p}$ will be smaller than the field size for $\mathbf{S_c}$. This is because the blocked field is smaller than the collimator jaw settings.

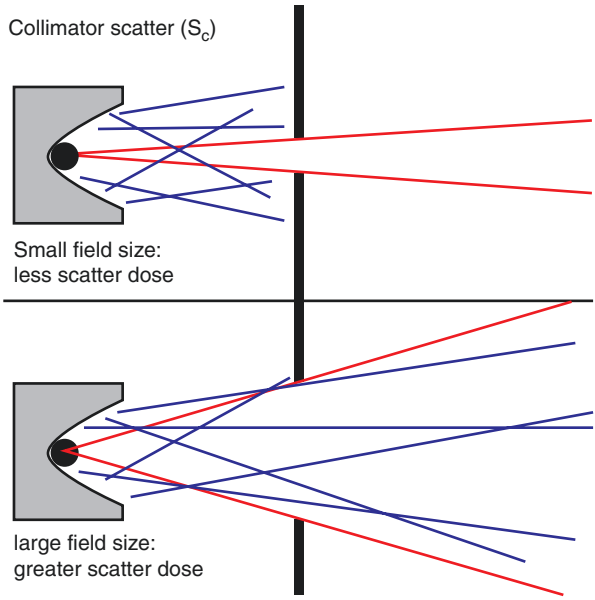


Fig. 8.2 Collimator scatter. Scatter increases with field size, as depicted above

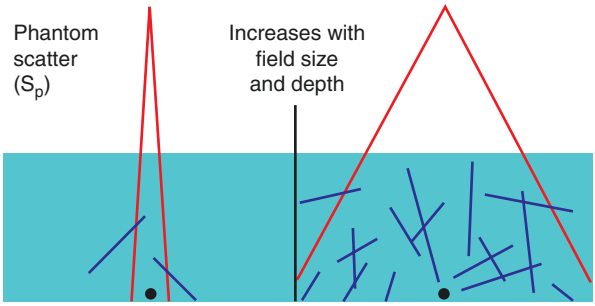


Fig. 8.3 Phantom scatter. Scatter increases with field size, as depicted above

- **Equivalent Squares** (**EqSq**)
  - $\mathbf{S_c}$ and $\mathbf{S_p}$ are measured with square fields.
    When treating with non-square fields, one must calculate the **equivalent square**.
  - What is the **equivalent square of a rectangle**?

$$EqSq = \frac{4A}{P} \tag{8.8}$$

- Where A is the area and P is the perimeter of the field.
  - What is the **equivalent square of a circle**?

$$EqSq = \sqrt{\pi} r \tag{8.9}$$

  - What is the **equivalent square** of a **complex-shaped field**?
    This may be calculated by the **Clarkson method**, described later in this chapter.

Beam Modifier Factors: WF and TF

- **Wedge factor** (**WF**) is a correction for having a wedge in the field. (For more details on wedges, see Chap. 9).
  - **Physical wedges** attenuate the beam, so **WF < 1.0** for a physical wedge.
  - **Nonphysical** (electronic or soft) **wedges** are software-defined, so they may or may not have a **WF** depending on how the machine is programmed.

$$\mathrm{WF} = \frac{\text{Dose with wedge}}{\text{Dose without wedge}} \tag{8.10}$$

- **Tray factor** (**TF**) is a correction for attenuation from the blocking tray (if physical blocks are used).
  - **TF < 1.0**.

$$\text{TF} = \frac{\text{Dose with tray}}{\text{Dose without tray}} \tag{8.11}$$

- **Other beam modifiers** (such as a beam spoiler) may have their own **attenuation factor**.

PDD Versus TMR (SSD Versus SAD)

- What is the difference? (Fig. 8.4).

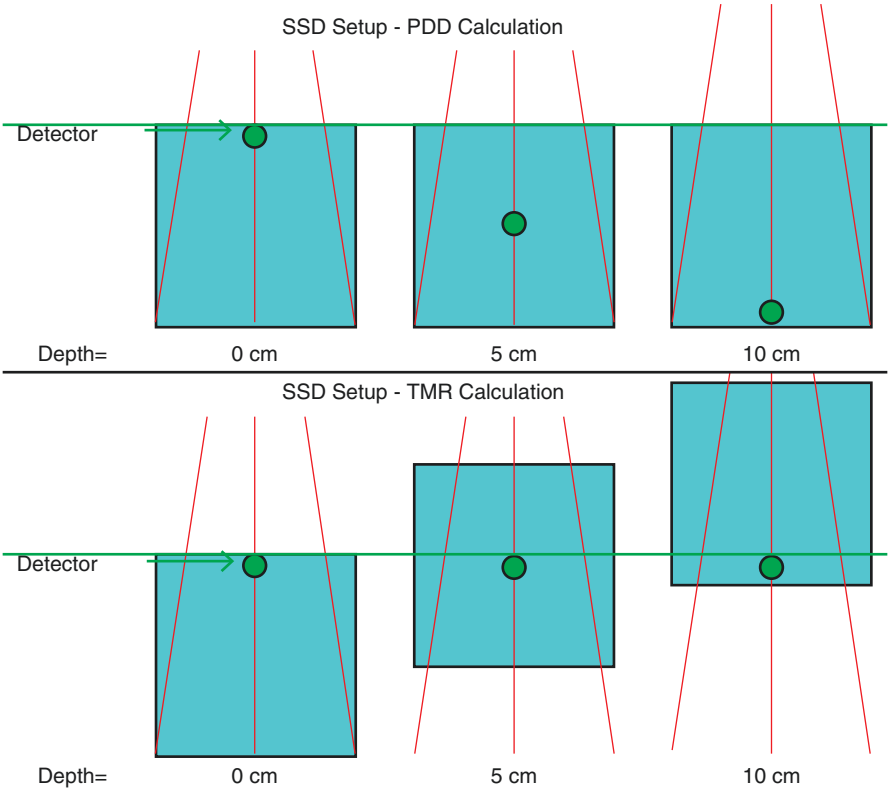


Fig. 8.4 PDD versus TMR. PDD is measured by moving the detector to different depths in a stationary phantom. Dose falls off due to both attenuation and distance (inverse square). TMR is measured by moving the phantom to different depths with a stationary detector. Dose falls off due to attenuation only

Hand Calculations (SAD Setup)

$$\text{Dose} = \text{MU} \times K \times \text{ISF} \times \text{TMR} \times S_c \times S_p \times \text{WF} \times \text{TF} \tag{8.12}$$

$$\text{MU} = \frac{\text{Desired_Dose}}{K \times \text{ISF} \times \text{TMR} \times S_c \times S_p \times \text{WF} \times \text{TF}} \tag{8.13}$$

- **K = Output Factor** (**cGy** per **MU**):
  - **K** = 1.0 if linac was calibrated to $\mathbf{d_{max}}$ at 100 SAD.
  - Otherwise may be different.
- **ISF** = Inverse square factor:

$$\text{ISF} = \left(\frac{\text{SAD}_{\text{ref}}}{\text{SAD}} \right)^2 \tag{8.14}$$

  - This is generally equal to 1.0 for **SAD** setup because **SAD** is a fixed number.
- $\mathbf{S_c}$, $\mathbf{S_p}$, **WF**, **and TF** are the same as for **SSD** setup.

Tissue-X-Ratios (TAR, TMR, TPR)

- These numbers are used for the calculation of **SAD** setups.
  - The generic term "**TXR**" is often used, because all three are very similar to each other.
- **TAR = Tissue-Air Ratio**

$$\text{TAR}(d) = \frac{\text{Dose at depth d in phantom}}{\text{Dose at same point in free air}} \tag{8.15}$$

  - **TAR** is mainly used for ^{60}Co because it is difficult to perform "free air" measurements at higher energies.
  - **TAR** is different from **TPR/TMR** because it includes **phantom scatter** ($\mathbf{S_p}$).

- **TMR = Tissue-Maximum Ratio**

$$\text{TMR}(d) = \frac{\text{Dose at depth } d \text{ in phantom}}{\text{Dose at depth } d_{\max} \text{ in phantom}} \tag{8.16}$$

  - **TMR** is always $\leq$**1**, since dose can never exceed $\mathbf{D_{max}}$.

- **TPR = Tissue-Phantom Ratio**

$$\mathrm{TPR}(d) = \frac{\text{Dose at depth } d \text{ in phantom}}{\text{Dose at depth } d_{\mathrm{ref}} \text{ in phantom}} \tag{8.17}$$

  - If $\mathbf{d_{ref} = d_{max}}$, then **TPR = TMR**.
- **BSF** = Back-Scatter Factor = **TAR**($\mathbf{d_{max}}$)
  - The $\mathbf{D_{max}}$ is a few percent higher in tissue than in air because back-scatter adds to maximum dose.
- **TXR**s can be easily interconverted:

$$\frac{\mathrm{TAR}(d)}{\mathrm{BSF}} = \mathrm{TMR}(d) = \mathrm{TPR}(d) \times \mathrm{TMR}(d_{\mathrm{ref}}) \tag{8.18}$$

Scatter-Air Ratio (SAR)

- This is a method to divide **TAR** into primary and scatter components. **SAR** is used for **Clarkson** calculations, described later.
- First measure **TAR**(**d**,**r**) at varying field size **r**.
- Extrapolate the **TAR** curve back to zero field size, $\mathbf{TAR_0}$ (**d**).
  - Since an infinitely narrow field should exclude scatter dose (see **narrow-beam attenuation**), $\mathbf{TAR_0}$ is assumed to equal the primary beam dose.
- **Calculating scatter contribution** (**SAR**):
  - Subtract the primary beam dose from the total dose to obtain scatter dose:

$$\mathrm{SAR}(d,r) = \mathrm{TAR}(d,\ r) - \mathrm{TAR}_0(d) \tag{8.19}$$

Rotational (Arc) Therapy (Fig. 8.5)

- Divide the arc into many equally spaced beam angles.
- Calculate a **TMR** for each beam angle.
- The average of all **TMR**s = total **TMR** for the arc.
- Photon arcs place the maximum dose at the isocenter, with dose falloff in all directions.
- Areas not covered by the arc will not have any entrance dose but may still receive exit dose. The amount of low-dose wash increases with the size of the field.

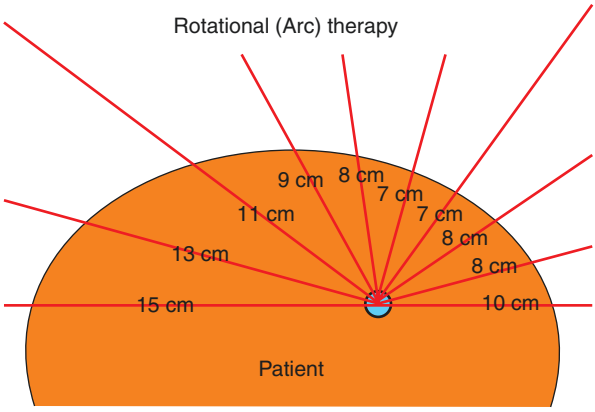


Fig. 8.5 Rotational arc therapy. Arc therapy may be approximated as the sum of many different beam angles

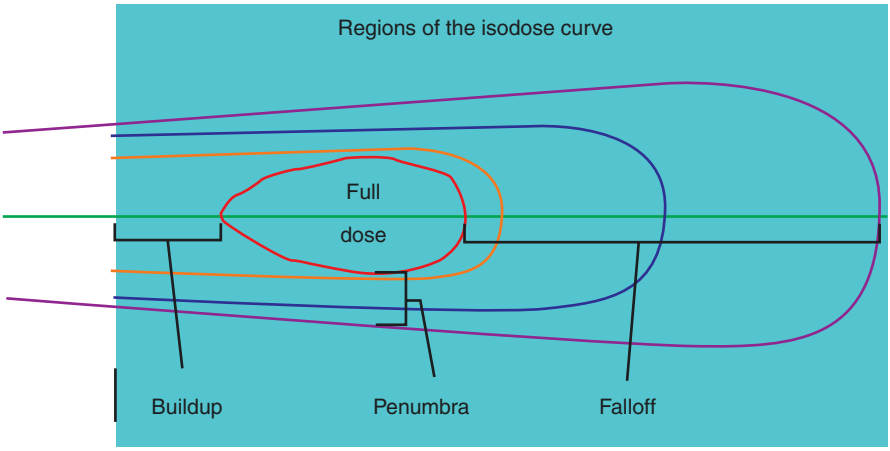


Fig. 8.6 Regions of the isodose curve. Isodose lines are a visual representation of calculated radiation dose. The areas of less than full dose can be divided into buildup, penumbra, and fall-off regions

Isodose Curves

- Isodose lines represent radiation dose in a 2D fashion, as shown in Fig. 8.6.

High Dose: The In-field Region

- The field edges are defined by the **50% isodose lines**.
  - That way if two abutting fields are matched to each other, 50% + 50% = 100%.
- The central field is defined by **80% of the field width**.
  - In a 10 cm × 10 cm field, the central 8 cm × 8 cm is flat and symmetrical, but the far-left and far-right 1 cm may get less than full dose.

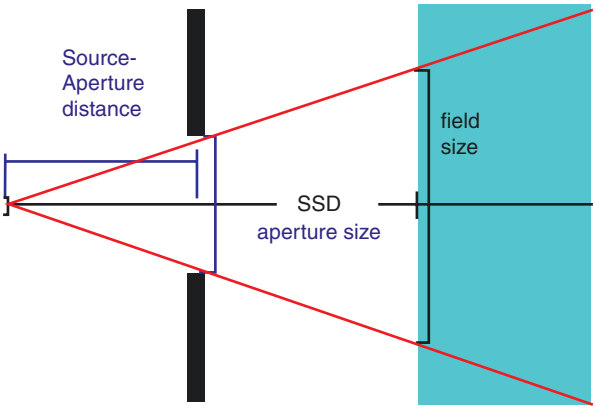


Fig. 8.7 De-magnification. When using a field shaping device, the aperture is always smaller than the field size. This ratio may be calculated by similar triangles

Field Shaping

- Refer to Chap. 9 for a detailed discussion of field weighting and wedges.
- **Field Shaping Apertures** (**Blocks**, **MLCs**)
  - Note that the opening (aperture) in a block is significantly smaller than the actual field size, due to de-magnification (Fig. 8.7).
  - De-magnification can be calculated with **similar triangles**.

$$\frac{x_1}{d_1} = \frac{x_2}{d_2} \tag{8.20}$$

  - Note that when using **MLCs**, the light field is slightly smaller than the actual radiation field.

    The **MLC**s completely block visible light, but radiation can leak through the leaf tips.

Clarkson Method

- A method of dose calculation for complex-shaped fields:
  - Divide field into many **rays**, and calculate **SAR** based on the length of each ray.

    Add **SAR** for each in-field ray section.

    Subtract **SAR** for each blocked ray section.
  - **SAR** for the field = average of all **SAR**s.
  - Note that this method is really calculating **phantom scatter** ($\mathbf{S_p}$). **TAR** includes $\mathbf{S_p}$ but not $\mathbf{S_c}$ (Fig. 8.8).

$$\mathrm{TAR}(d,r) = \mathrm{TAR}_0(d) + \mathrm{SAR}(d,\ r) \tag{8.21}$$

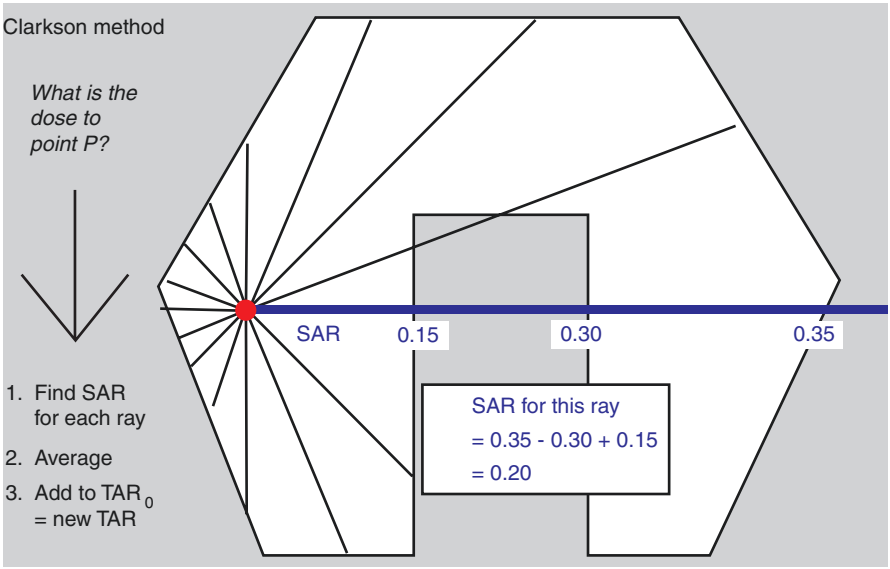


Fig. 8.8 The Clarkson method of scatter calculation. A complex-shaped field is divided into many small rays. Scatter (*SAR*) is calculated for each ray and then averaged

- The dose under a block (or MLC) can also be calculated by the Clarkson method:
  - **Transmission** ("Leakage"): **Jaws** ~ 0.1%, **Blocks or MLCs** ~ 1–3%.
    Multiply **TAR** $_0$ by the transmission factor to obtain the **primary beam dose**.
  - **Scatter**: Usually the predominant factor.
    SAR is calculated just like above to obtain the **scatter dose**.

How to Measure Scatter from an Area to a Point (Fig. 8.9)

Off-Axis Ratio (OAR)

- If dose is prescribed to a point outside of the central axis, an OAR must be included:

$$\mathrm{OAR}(x,d)=\frac{\text{Dose at offaxis point x at depth } d}{\text{Dose at central axis at depth } d} \tag{8.22}$$

- **OAR** is defined as 1.0 at the central axis.
- **OAR** changes with depth due to **flattening filter** effects:

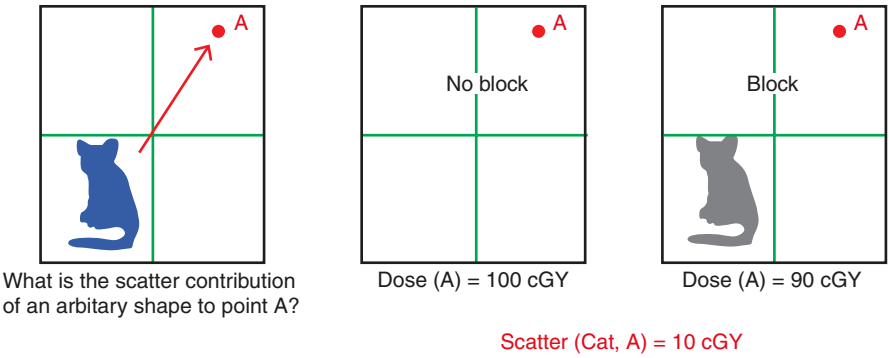
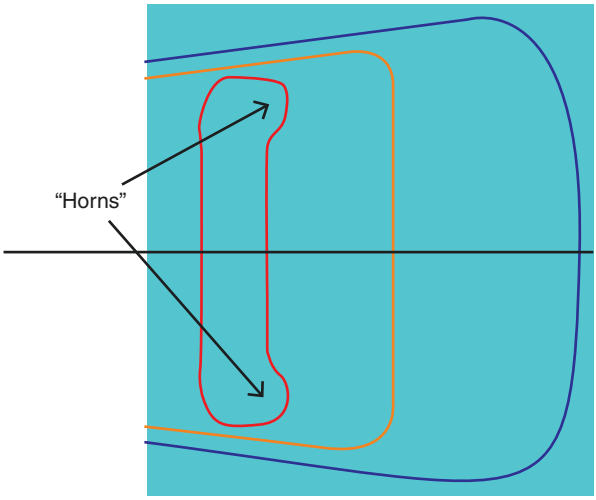


Fig. 8.9 Measuring out-of-field scatter dose. If you place a block in a large field and the measured dose changes by X cGy that means the blocked area must have contributed X cGy of scatter

Fig. 8.10 Photon beam horns. This figure is repeated from Chap. 7



  - The beam is **flat** (**OAR = 1.0**) at **10 cm depth**.
  - **Shallow**: Edges hotter than center (**OAR > 1.0**).
    - These hot spots are called the beam "horns."
  - **Deep**: Center hotter than edges (**OAR < 1.0**) (Fig. 8.10).
- In a **wedged field**:
  - **OAR < < 1.0** at the heel.
  - **OAR > > 1.0** at the toes (Fig. 8.11).

Superficial Dose: The Buildup Region

- Photons are indirectly ionizing and the dose is deposited by secondary electrons.

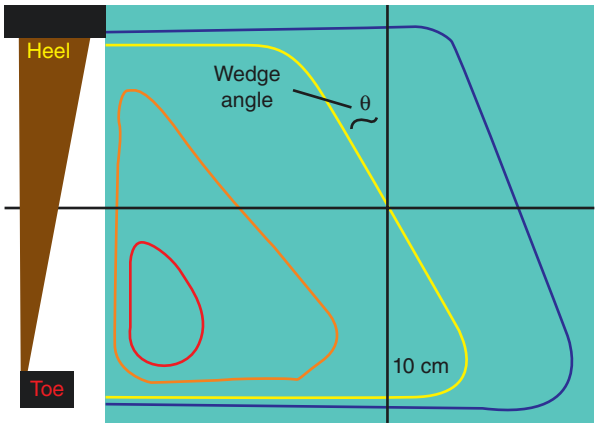


Fig. 8.11 A wedged field. This figure is repeated from Chap. 7

  - Most of the electrons generated at the surface deposit their dose at a depth corresponding to electron energy.
  - The higher the photon energy, the greater the range of secondary electrons.
  - Therefore, **surface dose** decreases with energy and is relatively low (~25–40%) for **6 MV** or higher.
- The region between the surface (d = 0) and d_{max} is called the **buildup** region, because dose is still building up.
  - **~0.5 cm** for **Co-60**
  - **~1.0 cm** for **4 MV**
  - **~1.5 cm** for **6 MV**
  - **~2.0–2.5 cm** for **10 MV**
  - **~3.0–3.5 cm** for **18 MV**
  - **~4.0–5.0 cm** for **25 MV**
- Ways to increase superficial dose:
  - **Decreased beam energy**.
  - **Increased field size** increases electron contamination of the field.
  - **Beam spoilers** (any material placed in the beam) to intentionally generate secondary electrons.
  - **Obliquity** (aka **Tangentiality**) decreases d_{max} and increases the surface dose.
  - **Bolus** moves the patient's skin to a nonzero depth.
- **Photons versus electrons**
  - Several aspects of superficial dose are **opposite** for photons and electrons.
    High Energy: less superficial dose for photons, more superficial dose for electrons.
    Small Field Size: less superficial dose for photons, more superficial dose for electrons.
  - See Chap. 10 for details.

Lateral Dose: The Penumbra Region

- **Penumbra** is the area at the beam edge where there is rapid lateral dose falloff.
- There are various measures of **penumbra**, such as distance from 90% to 50% isodose line, or 80–20% isodose line.

- There are two main contributions to **penumbra**:
- **Geometric penumbra** is due to finite source size.
  - This is important for Cobalt-60 (large source size).
  - It is much less of a factor for megavoltage linacs (Fig. 8.12).
- **Transmission penumbra** is due to transmission through the block or MLC edge.
  - This is most significant with **MLC**s.
  - Some **MLC**s are designed to intentionally broaden the penumbra to decrease the "stair step" phenomenon (Fig. 8.13a, b).
- **Physical penumbra** is due to physical processes depositing dose outside of the field edge.
  - **Charged particle disequilibrium**: Secondary electrons deposit dose laterally.
    This is the most important cause of penumbra for megavoltage photons.
    Penumbra is broader with **increased beam energy** and **decreased target density**.
    Therefore ≥10 MV is discouraged in the lung.
  - **Photon scatter** is the second most important factor.
  - **Photon leakage**, **electron contamination,** and **neutron contamination** are minor factors.

Rules of Thumb

- The goal of dose calculations is to determine how many **MU**s are required to deliver a given dose (**cGy**).
- **PDD** is used for **SSD** setup, **TXR** for **SAD** setup.
- **1 MU = 1 cGy** under reference conditions, by definition.
  - If your **MU** is much lower or higher than **cGy**, you need to figure out why.
- "**My MUs are a lot higher than my dose. Why**?"
  - Prescription SSD > reference SSD
  - Prescription depth > reference depth
  - Field size < 10 cm

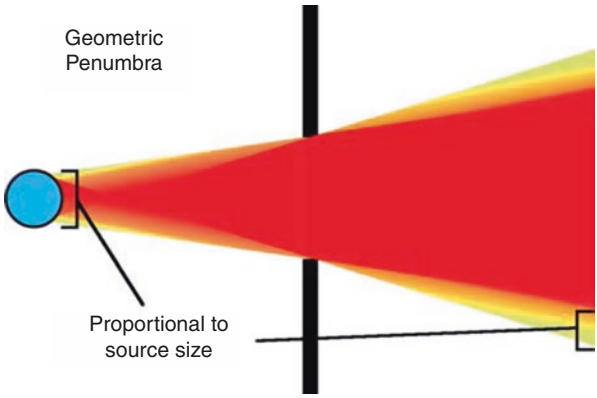


Fig. 8.12 Geometric penumbra. This blurring of the field edge is directly proportional to the physical size of the source. Linac targets are much smaller than Co-60 sources, so this is a minor effect for linacs

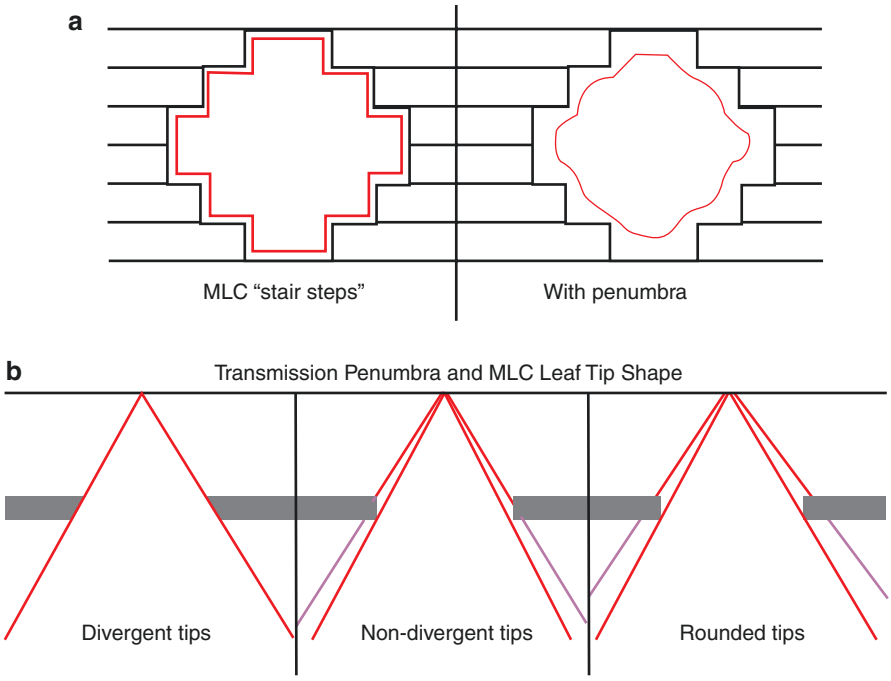


Fig. 8.13 (**a**, **b**) Transmission penumbra. If collimator tips do not diverge with the beam, differential transmission will slightly blur the field edge. In case of MLCs, this effect may be desirable, as it mitigates the "stair step" phenomenon

  - Wedges, IMRT, or other beam modifiers
  - Calculation error
- "**My MUs are a lot lower than my dose. Why**?"
  - Prescription SSD < reference SSD
  - Prescription depth < reference depth
  - Field size > 10 cm
  - Calculation error
- **Extended SSD Effects**
  - **ISF** is much lower – > you need much more **MU**.
  - **PDD** is slightly higher – > your dose falloff with depth is slightly less.
  - **Mayneord F-factor** calculates how large the **PDD** increase is. This should be no more than a few percent.
- **Dose Under a Block**
  - **Leakage Dose for 6 MV**
    Jaws ~ 0.1%
    Blocks, **MLCs ~ 1–3%**
  - **Scatter dose** may be much higher than that!
    This can be calculated by the Clarkson method or empirically measured.

Dosimetry of Photon Beams in a Patient

9

Introduction

Simple dose calculations are based on photon dose to water. When treating patients, dose corrections must be introduced to account for anatomic variations in shape and density. These dose correction techniques range from very simple rules to complex computer algorithms. Wedges and compensators may be used to correct for patient surface shape. Bolus may be used to increase the surface dose. Field-matching techniques may be used for treatments with closely abutting fields. Finally, International Commission on Radiation Units & Measurements (ICRU) specifications for target volumes and dose prescription are described.

Dose Calculation: Water Versus Patient

- Please refer to Chap. 8 (**Photon Dosimetry in Water**) for the basic dose calculation equations.
  - This chapter assumes that you already know how to calculate dose to water.
- Dose to patient is different from dose to water because:
  - Patient surface is not perfectly flat.
  - Patient tissue is not perfectly water equivalent: it contains air, bone, metal, and so on.
  - Clinical treatments often contain more than one radiation field. When matching fields, beam geometry must be matched to minimize hot and cold spots.

Corrections for Patient Contour

- Unlike a water phantom, patients have a non-flat surface. Therefore, corrections must be made for their contour.

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D. S. Chang et al., *Basic Radiotherapy Physics and Biology*,
https://doi.org/10.1007/978-3-030-61899-5_9

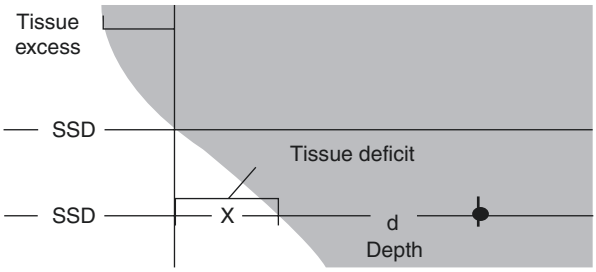


Fig. 9.1 Tissue excess and deficit. These values are measured as centimeters of deviation from a perfectly flat surface

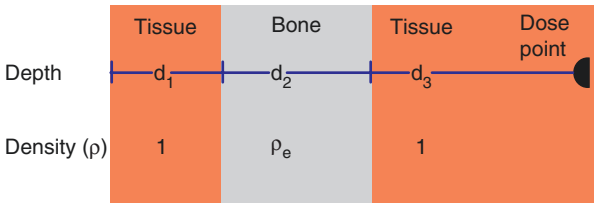


Fig. 9.2 Inhomogeneity correction. An inhomogeneity can be characterized by its location (depth), density, and thickness as depicted above

- The difference between a flat surface and the patient surface is known as "tissue deficit" or "tissue excess."
  - **x = tissue excess** (negative number for tissue deficit)
  - **d = depth in tissue**
  - **r = field size** (Fig. 9.1)
- Several different methods exist to calculate the dose with an irregular surface.

Inhomogeneity Corrections

- High-density tissue (bone) increases attenuation, while low-density tissue (lung) decreases attenuation.
- Therefore, the dose distal to an inhomogeneity will be different than the dose in a homogeneous phantom (Fig. 9.2).

Classical Methods

- Uses beam data measured in water, and applies simple correction factors for irregularities in surface contour and inhomogeneities in tissue.
- These methods are rarely used in modern era radiotherapy.
- **Irregular contour corrections**:
  - **Effective source to skin distance (SSD) method**: uses a SSD/percent depth dose (PDD) calculation and corrects for depth in tissue.
  - **Tissue air ratio (TAR) ratio method**: uses a TAR correction factor based on the thickness of tissue excess or tissue deficit.
  - **Isodose shift method**: uses a "shift factor" to move the isodose lines based on tissue excess or deficit.

- **Inhomogeneity corrections**:
  - **TAR ratio method**: uses the "radiographic depth" to calculate a new TAR.
  - **Batho power law method**: calculates TAR based on an exponential function of depth.
  - **Isodose shift method**: uses a "shift factor" based on the thickness and nature of the inhomogeneity.

Model-Based Calculations

- Modern treatment planning systems use computer models to calculate dose (see Chap. 16).
  - These are all based on **Monte Carlo** (**MC**)-simulated pencil beam kernels.
- In order from least sophisticated to most sophisticated, the common computer models are as follows:
  - **Pencil beam** (**PB**) **kernel**: only accounts for central axis of the beam.
  - **Superposition/convolution** method: also accounts for lateral inhomogeneities.
  - **Collapsed cone** method: also accounts for lateral inhomogeneities.
    Analytical anisotropic algorithm (AAA)
    Accuros
  - **Monte Carlo**: the most accurate and computationally intensive algorithm.
- The details of computer-based models are discussed further in Chap. 16, but finer details are beyond the scope of this review book.

Inhomogeneity Perturbations

- At an interface between "less dense" and "more dense," there is a loss of **electronic equilibrium** needed to calculate dose in medium.
  - High-density tissue generates more secondary electrons, and low-density tissue generates fewer secondary electrons (Fig. 9.3).
- The high-density side is relatively **underdosed** because there are not enough electrons coming from the low-density side.
  - **Tissue next to lung/air may be underdosed**.

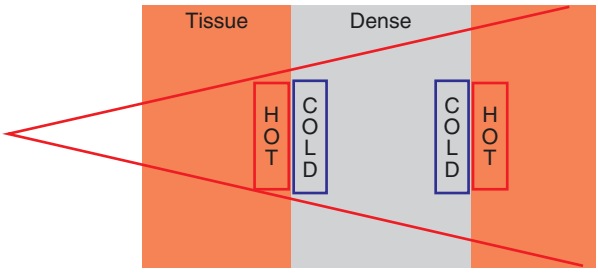


Fig. 9.3 Interface effects. When a photon beam encounters an inhomogeneity, hot and cold spots occur due to differences in secondary electron production

- The low-density side is relatively **overdosed** because there are too many electrons coming from the high-density side.
  - **Tissue next to bone/metal may be overdosed**.
  - Photon scatter may also contribute to this hot spot, especially with a metal/tissue interface.
- Doses at an inhomogeneity interface are difficult to calculate or measure accurately, but several of the algorithms described above can handle inhomogeneities.

Parallel Opposed Fields

- Evenly weighted parallel opposed fields are the simplest method to create a "uniform" dose.
- **Tissue lateral effect** (aka hourglass effect): dose is always higher superficially than at depth.
  - Larger **separation** increases the max dose, as $\mathbf{D_{max}}$ increases faster than $\mathbf{D_{exit}}$ decreases.
- **Depth = Separation/2**
  - This is a common test-taking mistake.
  - Always know whether you are using **depth** or **separation**, or you will be off by a factor of 2 (Fig. 9.4).
- **How to calculate the lateral dose**?

$$
\begin{aligned}
D_{\max}\left(\text{beam}_1\right) &= \frac{100\%}{\text{PDD}\left(d_{\text{midplane}}\right)} \\
D_{\text{exit}}\left(\text{beam}_2\right) &= \frac{\text{PDD}\left(d_{\text{exit}}\right)}{\text{PDD}\left(d_{\text{midplane}}\right)} \\
D_{\text{total}} &= \frac{D_{\max}\left(\text{beam}_1\right) + D_{\text{exit}}\left(\text{beam}_2\right)}{2}
\end{aligned}
\tag{9.1}
$$

- **How to keep $\mathbf{D_{max}}$ low**: (and what are the tradeoffs?)
  - **Increased beam energy**:
    You lose superficial dose.
  - **Extend SSD**:
    Mayneord F-factor works in your favor.
    More time consuming setup.
  - **Add more fields**:
    A three- or four-field combination will reduce the superficial dose compared to AP/PA, at the cost of increasing complexity of treatment.

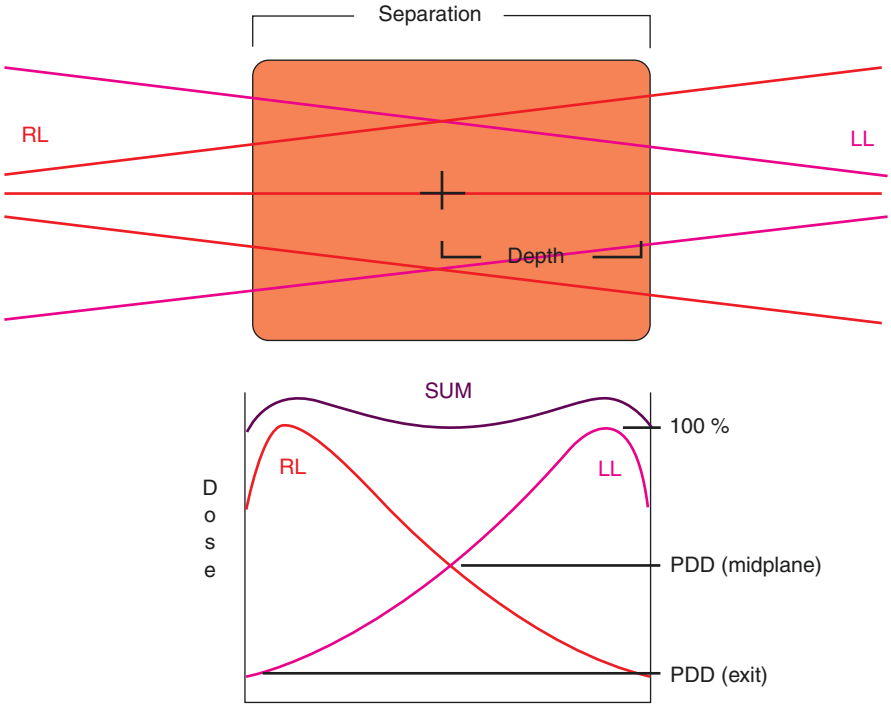


Fig. 9.4 Tissue lateral effect. In a radiation treatment with parallel opposed beams, the peripheral dose is always higher than the central dose. This effect increases with separation and decreases with beam energy

Wedges

- A **wedge** produces a sloped isodose distribution with less dose on one side (the heel) and more dose on the other (the toe).
  - A **physical wedge** is a wedge-shaped piece of metal.
  - A **nonphysical wedge** or **soft-wedge** is a software program that moves the collimator jaw in a calibrated fashion to produce a wedge-shaped dose distribution.

    Each linac manufacturer has a unique soft wedge with a different proprietary name, enhanced dynamic wedge, EDW by Varian, Virtual wedge, VW by Siemens and Universal wedge (UW) by Elekta.
- **Physical wedges** generate **scatter. Nonphysical wedges** do not.
  - Scatter increases dose outside the field, so any organs sensitive to very low dose are at increased risk (such as the contralateral breast during whole-breast RT).
  - This may also slightly increase surface dose.
- **Physical wedges** also cause **beam hardening**, so the angle of the isodose lines decreases at very deep depths (Fig. 9.5).

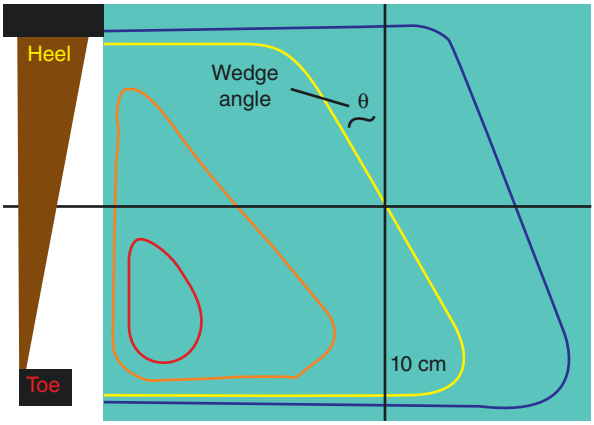


Fig. 9.5 Wedge angle. Wedge angle is defined by the angle between the wedged isodose line and a straight line at 10 cm depth. This figure is repeated from Chap. 7

- **Wedge angle** is defined as depicted in Fig. 9.5.
- **Wedge factor** (**WF**) is defined as the ratio of dose with wedge to dose without wedge for the same field.
  - WF depends on beam energy, wedge angle, field size, and depth.
  - **Be very careful with WF**! Any error can cause a serious dosimetric error and mistreatment.
- **Wedges** may be used with parallel opposed fields to compensate for a sloping patient contour:
  - Breast tangents
  - Neck laterals
  - Thorax AP/PA
- **How to judge the wedge angle**?
  - **Underwedged** = 1 large hot spot at the heel.
  - **Overwedged** = 2 large hot spots at the toes.
  - **Optimal wedge** = 3 small hot spots at toes and heel (Fig. 9.6).
  - **Intentional underwedging** can increase the superficial dose.
    This is commonly done in larynx fields to avoid underdosing the anterior commissure.
  - **Wedges** can improve dose homogeneity in parallel opposed fields (such as whole breast), but they are strictly inferior to compensators or field-in-field technique.
- **Wedge pairs** are a very common radiotherapy beam arrangement.
  - Remember the direction of the wedges: **heels together** (there is no place like home) (Fig. 9.7).
  - Simple equation for **optimal wedge angle**:

$$\text{Wedge Angle} = \frac{(180 - \text{Hinge Angle})}{2} \tag{9.2}$$

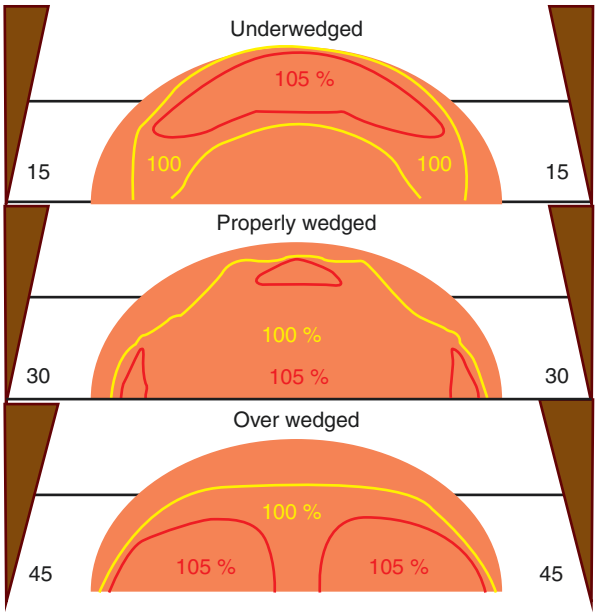


Fig. 9.6 Hot spots and wedging. The "optimal" wedge angle produces three very small hot spots, while "underwedging" or "overwedging" results in much larger hot spots

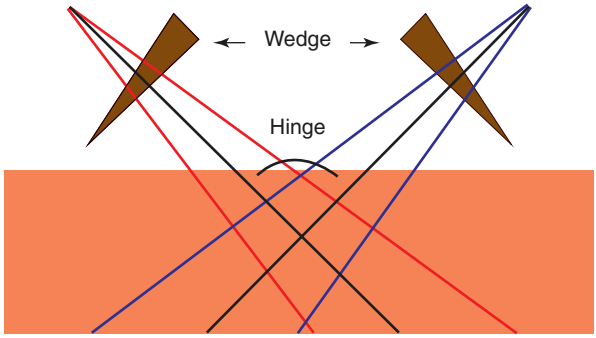


Fig. 9.7 Wedge pair. This technique is used to create a homogeneous field with non-opposed beams

- **A three-field box** (wedged laterals and PA) uses wedges to compensate for an "unbalanced" beam (Fig. 9.8).
  - Heels toward the "unbalanced" beam.
  - Optimal wedge angle depends on many factors including beam weights. No easy equation, use computer planning to determine the angle.

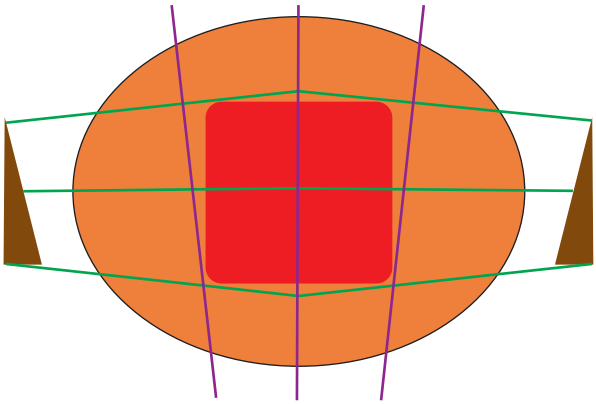


Fig. 9.8 Three-field box. This technique is used to treat a box-shaped field while avoiding the use of an anterior beam. This may decrease bowel dose when treating the pelvic tumors

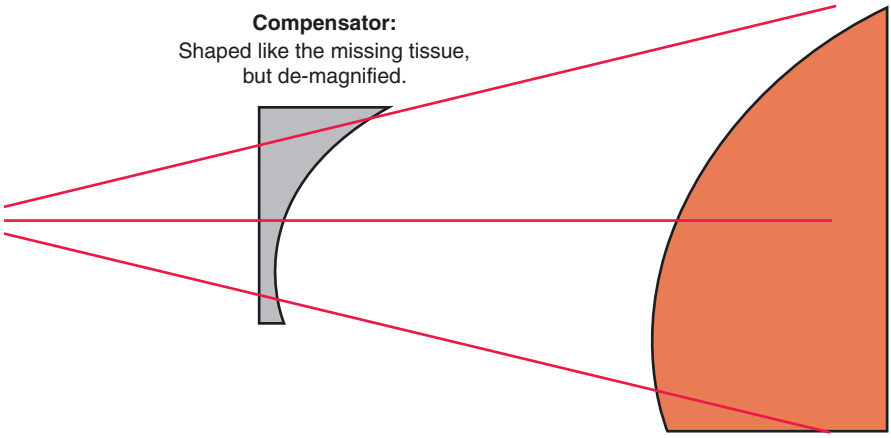


Fig. 9.9 Compensators. The purpose of a compensator is to make up for tissue deficit

Mixed Modality Therapy (Photon/Electron Mix)

- Refer to Chap. 10 (**Electron Dosimetry**) for details.

Compensators

- Compensators are used to improve dose homogeneity by compensating for tissue deficit.
  - May be made of tissue-equivalent material (i.e., **Lucite**) or high-density material (i.e., **brass**, **cerrobend**, **or lead**) (Fig. 9.9).
- Compensator thickness is equal to the **tissue deficit** multiplied by the **ratio of attenuation factors**.

  - For a tissue-equivalent compensator: 1 cm tissue deficit = 1 cm compensator thickness.
  - For a high-density compensator: 1 cm tissue deficit = significantly less compensator thickness.
- **Like blocks**, compensators must be **demagnified** by the ratio of source-to-compensator distance to SSD.
- "**Electronic compensators**" use MLCs and multiple segments to create a fluence map, approximating the dose distribution from a physical compensator.

Field Matching

- The **dose at a field edge is 50**% by definition. Therefore, if two field edges were perfectly aligned, there should be a uniform 100% dose at the junction.
  - However, divergent field edges will result in cold spots and hot spots.
- The simplest way to match two fields is to use **half-beam blocks**.
  - This is known as **mono-isocentric technique** because the isocenter is placed at the field junction.
  - Limitation: you can only use half of your maximum field size (Fig. 9.10).
- Matching two parallel PA fields requires a **skin gap** due to divergence. Calculate using similar triangles as shown in Fig. 9.11.

$$g = d \times \frac{y_1}{\mathrm{SSD}_1} + d \times \frac{y_2}{\mathrm{SSD}_2} \tag{9.3}$$

  - Note that if source to axis distance (**SAD**) technique is used, **SAD** may be substituted for **SSD** and the above equation is still valid.
- Beams may also be rotated to match divergence (Fig. 9.12).

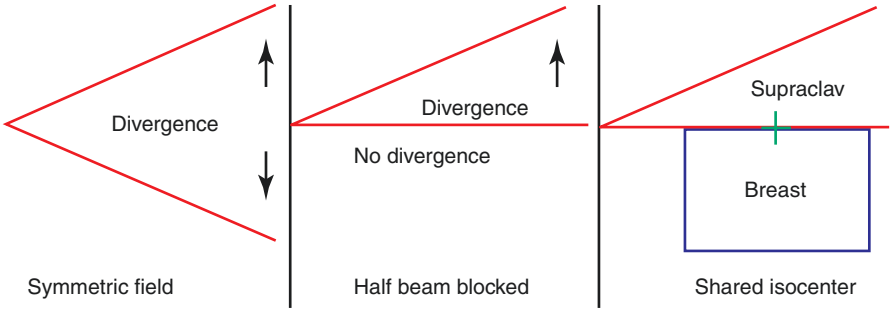


Fig. 9.10 Half-beam block. Since there is no divergence at the isocenter, the simplest way to eliminate divergence is to block half of the beam

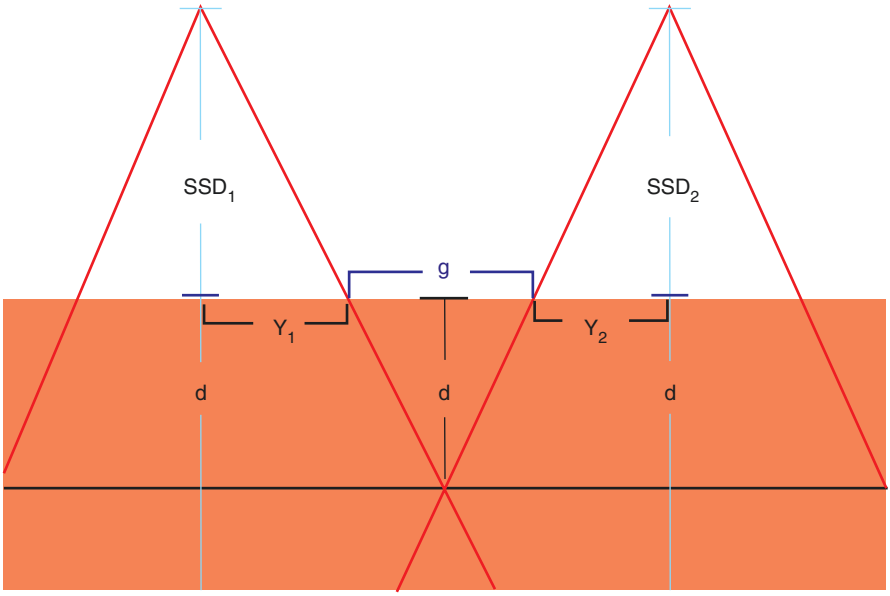
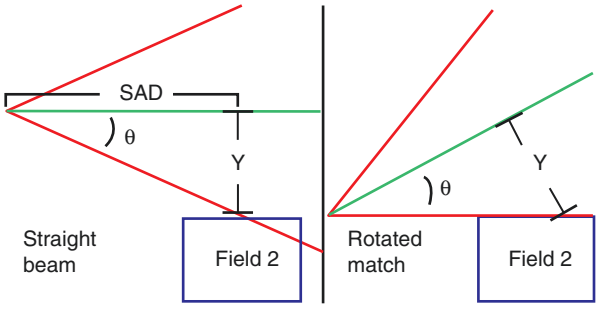


Fig. 9.11 Parallel field matching. When treating a field length much larger than your maximum field size, you will need to match two parallel fields. This will require a skin gap (*g*). The size of this gap may be calculated by Eq. 9.8

Fig. 9.12 Rotational match. In order to eliminate beam divergence of angle θ, the beam angle may be rotated by angle θ



$$\theta = \left(\arctan\left(\frac{y}{\mathrm{SAD}} \right) \right) \tag{9.4}$$

Craniospinal Field Matching (Fig. 9.13)

- Because the cranial fields are noncoplanar with the spine field, both **collimator rotation** and **couch kick** are required.
  - Both of these rotations are performed on the brain field. The spine field remains a straight PA.
  - **Collimator rotation** matches the anterior upward divergence of the spine field.

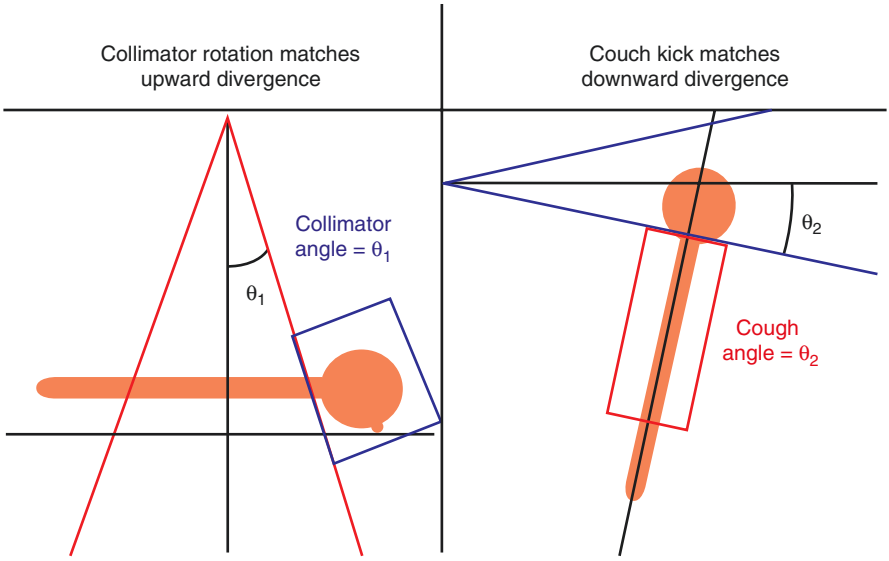


Fig. 9.13 Craniospinal field matching. A collimator rotation on the brain field is used to match the upward divergence of the spine field. A couch kick on the brain field is used to eliminate its downward divergence

$$\theta_1 = \arctan\left(\frac{\text{spine } y_1}{\text{SAD}}\right) \tag{9.5}$$

– **Couch kick** matches the lateral downward divergence of the brain fields.

$$\theta_2 = \arctan\left(\frac{\text{brain } y_2}{\text{SAD}}\right) \tag{9.6}$$

- An **additional gap** may be used to ensure that there is no overlap (the exact number of millimeters is institution dependent, based on personal experience and machine factors).
- **Feathering** is a dose smearing process in which the field junction is moved in between fractions so that any hot or cold spots are "smeared out" (Fig. 9.14).

Maximizing Superficial Dose

- The **skin sparing** effect of megavoltage photons is useful unless you are trying to treat the skin.
- Skin dose is a function of head design, SSD, energy, field size, medium in the beam, and angle of the beam.

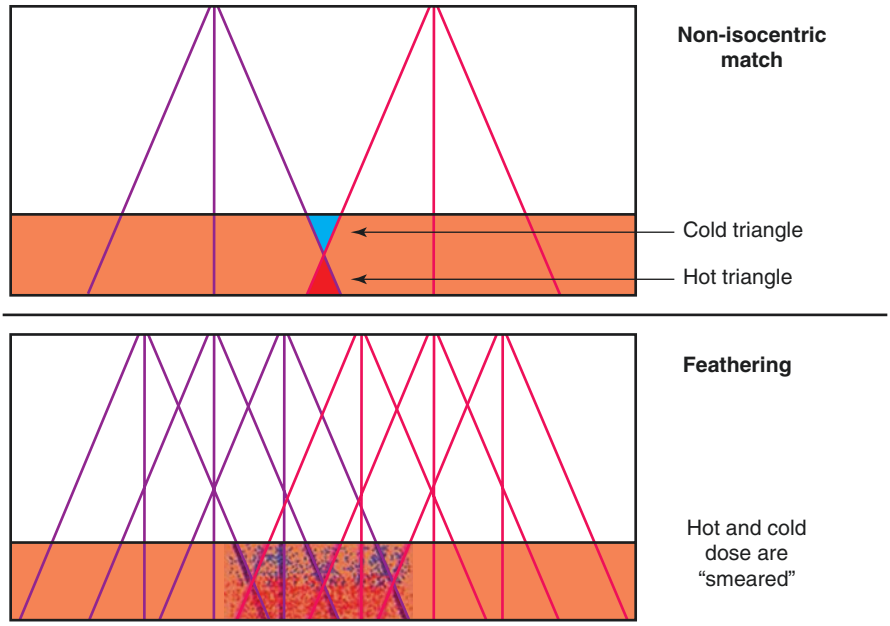


Fig. 9.14 Feathering. A non-isocentric match results in a "cold triangle" and a "hot triangle." The field junction is moved in between fractions, causing the mismatch to smear out over a larger area. This decreases the magnitude of underdose or overdose

- **How do you increase the superficial dose**?
  - **Low energy** (**Co-60**, **4MV**) can increase superficial dose but many clinics do not have such low-energy beams.
  - **Isocentric** (**SAD**) treatments usually give higher surface dose compared to **SSD** techniques.
  - Intentional **electron contamination** of a photon beam:
    Very large field size: electron scatter from collimator jaws.
    Beam spoiler: a plate of material (Lexan, etc.) is placed into the field to generate secondary electrons.
  - **Bolus** moves the buildup region outside the patient (Fig. 9.15).
- **Bolus materials** in order of increasing tissue equivalence:
  - Rice bags
  - Wet gauze
  - Wet towels
  - Superflab
  - Custom wax bolus
  - Immersion in water
- **Obliquity** (also known as **tangentiality**):
  - Oblique beam incidence will increase the surface dose:
    Secondary electrons take the path of least resistance and go toward air.
  - This is most relevant to breast and chestwall tangents (Fig. 9.16).

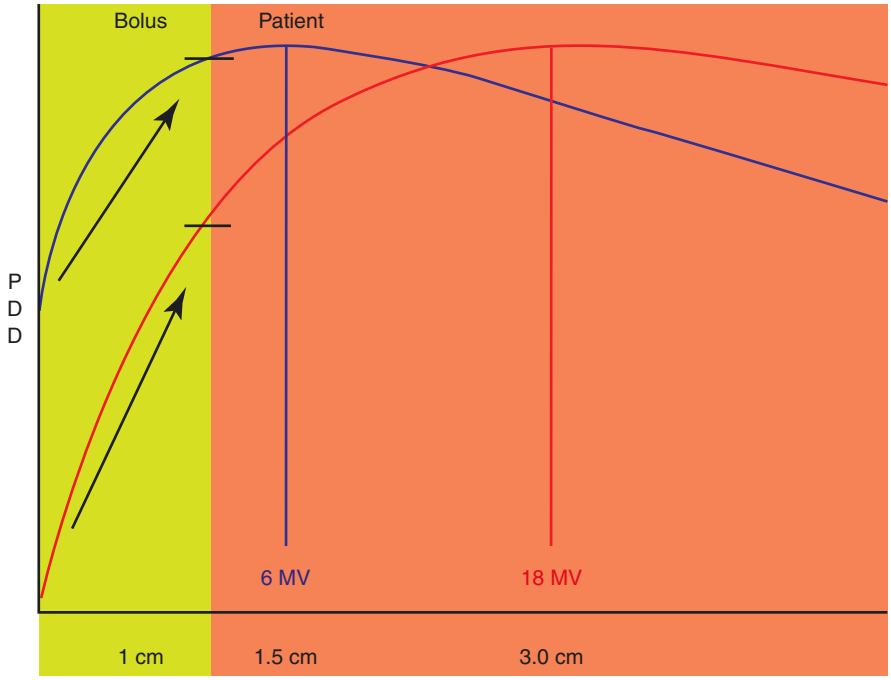


Fig. 9.15 Bolus effect. Placing bolus material on top of the skin allows the dose buildup to occur inside the bolus, increasing skin dose

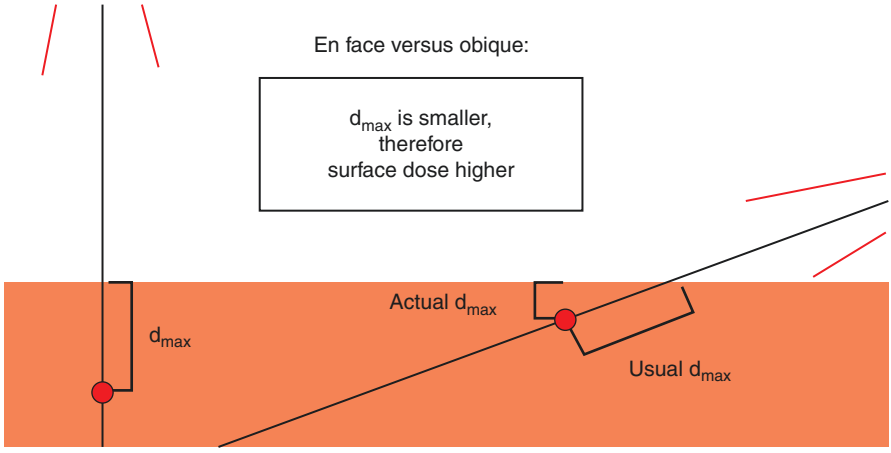


Fig. 9.16 Obliquity effect. D_{max} occurs at a shallower depth than usual, as depicted above

$$\text{Obliquity Factor}\ (\text{OF}) = \frac{\text{Surface Dose}\ (\text{oblique})}{\text{Surface Dose}\ (\text{en face})} \tag{9.7}$$

– Obliquity factor is one reason why the top of the head gets the worst alopecia after whole-brain RT ("reverse mohawk effect").

Dose Specification (ICRU 50 and 62)

- **ICRU 50** defined **GTV**, **CTV**, **PTV**, **TV,** and **IV**:
  - Gross target volume (**GTV**): visually, palpably, or radiographically apparent disease that is intended to be treated.
  - Clinical target volume (**CTV**): volume suspected to harbor microscopic (subclinical) disease, which includes "margin around GTV" and "elective CTVs."
  - Planning target volume (**PTV**): CTV plus margin for setup error.
  - Treated volume (**TV**): volume encompassed by an isodose line appropriate for treatment of disease (ideally a high isodose line).
  - Irradiated volume (**IV**): volume encompassed by an isodose line appropriate for normal tissue toxicity (ideally a low isodose line).
  - Dose in conformal therapy should be reported to an **ICRU reference point**, as well as minimum and maximum PTV dose.
  - **ICRU reference point** requirements:
    Clinically relevant and representative of dose throughout the PTV.
    Easy to define in an unambiguous way.
    Located in an area where dose can be accurately calculated.
    Located away from penumbra or steep dose gradients.
  - The **prescription dose** may be expressed as a percentage of the **reference point dose**.
    "Prescribed to the 95% isodose line."
  - The **PTV volume dose** should be within 95–107% of prescription dose (when possible).
- **ICRU 62** introduced several new concepts:
  - Internal margin (**IM**): physiologic variations in shape and position.
  - Internal target volume (**ITV**) = **CTV** + **IM**.
  - Setup margin (**SM**): uncertainty of dose calculation, therapy machine alignment, and patient setup.
  - Planning risk volume (**PRV**): organs at risk (OARs) plus **IM** and **SM**.
    Combination of margins should be based on clinical appropriateness, and do not use the same margins for every patient.
  - **CI** = Conformity index = Volume (**TV**)/Volume (**PTV**).
    CI is a simple ratio and does not guarantee that the **TV** encompasses the **PTV**.
- The concept of **ICRU reference point** is not valid for **IMRT** because **IMRT** fluence and volume dose are nonhomogeneous.

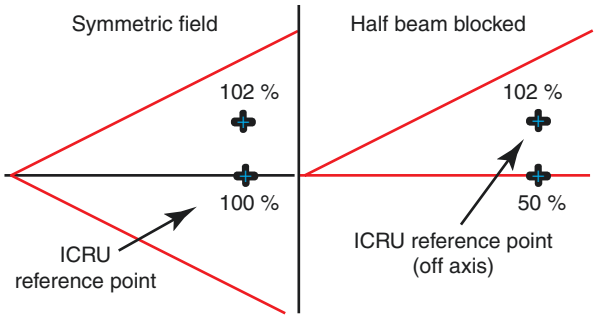


Fig. 9.17 Off-axis reference point. When treating with a half-beam block, the isocenter can no longer be used as a dose reference point as it is on the block edge. Instead, an off-axis point must be chosen as a reference point

  - Instead of reporting an ICRU reference dose, report volume doses (DVHs for target volumes and organs at risk) instead.

Dose Specification for Half-Beam Blocks

- Half-beam blocks are commonly used to eliminate divergence and simplify field matching (Fig. 9.17).
- The prescription point (**ICRU reference point**) cannot be at the isocenter because the field edge is at isocenter.
  - The dose would be 50% with a steep gradient.
- Therefore, the dose must be prescribed to an off-axis point.
  - Use off-axis ratio to calculate off-axis dose.
  - See Chap. 8 for details.

Prescribing and Delivering Dose (ICRU 50/62)

- This is the standard way to prescribe and report dose to a non-IMRT plan.
- **Prescription dose** should be defined as cGy/fraction (fxn) and number of fractions (i.e., 200 cGy * 30 fxn = 6000 cGy).
- The **prescription dose** should be expressed as a percentage of the **dose to ICRU reference point** ($\mathbf{D_{ref}}$).
  - For example, "We prescribed 200 cGy/fxn to the 90% isodose line."
  - The dose to $\mathbf{D_{ref}}$ can be calculated as follows:

$$D_{\text{ref}} = \frac{\text{Prescription Dose}}{\text{Prescription IDL}} \tag{9.8}$$

  - **Example**: 200 cGy/fxn prescribed to the 90% isodose line (IDL) means that D_{ref} = 222 cGy/fxn.
- Each beam should contribute a portion of the **reference dose**, and this defines the **beam weight**.

$$D_{\text{ref}} = D_1 + D_2 + \cdots + D_i$$
$$D_{\text{i}} = D_{\text{ref}} \times \frac{\text{Beam Weight (i)}}{\text{Total Beam Weight}} \tag{9.9}$$

  - **Example**: D_{ref} = 222 cGy, therefore:
    To treat with equally weighted AP/PA:
    D_{AP} = 111 cGy, D_{PA} = 111 cGy.
    To treat with equally weighted four-field box:
    D_{AP} = 55.5 cGy, D_{PA} = 55.5 cGy.
    $D_{Rt\ Lat}$ = 55.5 cGy, $D_{Lt\ Lat}$ = 55.5 cGy.

- Finally, calculate **MU** for each beam to deliver the desired dose:
  - **Example**: D_{AP} = 111 cGy, D_{PA} = 111 cGy:
    If the AP beam delivers 1.0 cGy/MU, it needs 111 MU.
    If the PA beam delivers 1.11 cGy/MU, it needs 100 MU.

Dose Delivery Accuracy and Precision

- Linacs are generally calibrated to ~**2 mm** and **2**% precision, except for stereotactic setups which are **1 mm**.
- Please refer to Chap. 13 for details on linac precision.

Rules of Thumb

- **Irregular patient contour**:
  - **Tissue deficit** moves IDLs **away from surface**.
  - **Tissue surplus** moves IDLs **toward surface**.
- **High-density structures** (bone, metal):
  - **Adjacent hot spot** due to secondary electrons and scatter.
  - **Distal cold dose** due to attenuation.
- **Low-density structures** (lung, air):
  - **Adjacent cold spot** due to loss of secondary electrons and scatter (buildup effect).
  - **Distal hot beam** due to decreased attenuation.
- **Tissue lateral effect**:
  - Lateral hot spots with any parallel opposed plan.
  - Increases with separation, decreases with beam energy.
  - If it is too hot, add more beams.
- **Wedges**:
  - **Toes hot = overwedged**.
  - **Heel hot = underwedged**.

  - **Wedge pair**:

$$\text{Wedge} = \frac{\left(180 - \text{Hinge}\right)}{2}$$

- **Matching**:
  - **Skin gap = similar triangles**, use SSD if SSD setup and SAD if SAD setup.
  - **Angled match**:

$$\theta = \left(\arctan\left(\frac{y}{\text{SAD}}\right)\right)$$

- **Craniospinal**:
  Collimator rotation matches upward divergence of spine fields.
  Couch kick matches downward divergence of brain fields.

- **Oblique fields**: Decreased $\mathbf{d_{max}}$, increased surface dose.

Dosimetry of Electron Beams

10

Introduction

The electron is a charged particle with a finite range directly proportional to its energy. Electron treatments are limited to more superficial depths than photons. With electrons, surface dose increases with energy, unlike photons. Simple dose calculations are based on electron dose to water, using source-to-surface distance (SSD) setup geometry. Density inhomogeneities greatly alter electron dose distributions. Electrons take the path of least resistance, increasing the dose to low-density structures that abut high-density structures. Bolus and spoilers can increase superficial dose and decrease range. Obliquity can greatly increase superficial dose and decrease range.

Definitions

- **D** = Dose
- **d** = Depth (sometimes called z)
- $\mathbf{D_{max}}$ = Maximum dose to a point, defined as = 100%
- $\mathbf{d_{max}}$ = The depth of $\mathbf{D_{max}}$ (sometimes called $\mathbf{z_{max}}$)
- **SSD** = Source-to-surface distance
- **PDD** = Percent depth dose
- **MU** = Monitor units
- **K** = Output factor
- **ISF** = Inverse-square factor
- **OF** = Obliquity factor
- $\mathbf{R_{90}}$ = Distance of 90% dose from surface
- $\mathbf{R_{50}}$ = Distance of 50% dose from surface
- $\mathbf{R_p}$ = Practical range
- $\mathbf{R_{max}}$ = Maximum range

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Dose: Hand Calculations

$$\text{Dose} = \text{MU} \times K \times \text{ISF} \times \text{PDD} \times \text{OF}$$
$$\text{MU} = \frac{\text{Desired_Dose}}{K \times \text{ISF} \times \text{PDD} \times \text{OF}} \quad (10.1)$$

- **K = Output factor = 1.0 cGy/MU** for standard electron cone and large field size.
  - This makes electrons very easy to calculate.
  - **K** may change with electron cone (applicator factor) and with small cutouts (field size).
  - When in doubt, **K** should be measured for a given applicator-cutout combination (empiric **K**).
  - **ISF** is different from photons due to **effective SSD**—this is discussed later in the chapter.
  - **PDD** is a prescription isodose line, for example, "we prescribed **200 cGy** to the **90%** isodose line."
  - **OF = Obliquity factor**, an increase in dose that occurs with oblique beam entry.

Electrons: Range

- Electrons are **charged particles**. Therefore, as they interact with medium (tissue, water, etc.), they slow down and lose energy, eventually coming to a stop.
  - Refer to Chap. 5 for more details on charged particle interactions.
- The path of an electron can be measured in two different ways (Fig. 10.1).
  - **Range** (**CSDA**): the straight-line distance traveled by the electron, equal to clinical **depth**.
  - **Path length**: actual length of the path, always much longer than range.
    Imagine pulling at a spring until it stretches out straight. Its length would increase a lot.
- Each electron in a beam takes a unique path, so range varies from electron to electron.
  - Different **range** values as shown in Fig. 10.2 are stated depending on usage.

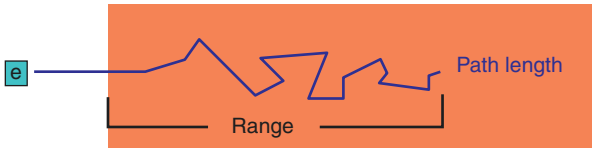


Fig. 10.1 Range and path length: because range is measured in a straight line, it is always much smaller than path length

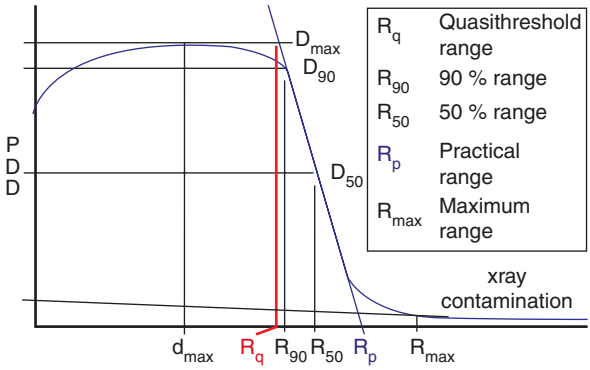


Fig. 10.2 Electron range metrics. R_{90} and R_{50} are defined by the depth of the 90 and 50% isodose lines. A straight line is drawn between R_{90} and R_{50} and used to calculate extrapolation values. Extrapolating back to 100% gives the R_q, while extrapolating forward to 0% gives the R_p. R_{max} is the maximum range of electrons, after which dose is entirely due to Bremsstrahlung X-rays

Electrons: Shape of PDD Curve

- Electrons are directly ionizing, so there is no charged particle buildup like with photons.
- So, why is the surface dose not 100%? (Note: it is more like 75–95%.)
  - **Multiple scattering** causes an increase in electron fluence as electrons move in the medium which increases dose at depth, so the maximum dose is higher than the surface dose (Fig. 10.3).
- After $\mathbf{d_{max}}$, dose decreases as electrons loose enrgy continuously reaching the end of their range ($\mathbf{R_{50}}$, $\mathbf{R_p}$, $\mathbf{R_{max}}$).
  - Low-energy electrons have a very sharp distal dose falloff, while higher energy electrons have a more gradual distal falloff (Fig. 10.4).
- Beyond $\mathbf{R_{max}}$, dose decreases to a low but nonzero number which is due to bremsstrahlung production.
  - **Bremsstrahlung X-rays** (<5% of electron dose) and energy dependent (see Fig. 10.4).
  - Bremstrahlung dose increases with electron energy and with materials in the electron beam. The **scattering foil** is a major contributor to bremsstrahlung.
  - Bremsstrahlung dose is greatest at central axis and less at field edges.

Electrons: Energy Spectrum and Range

- The nominal energy of an electron beam is equal to the electron energy **in the accelerator**. This is a mono-energetic value.
  - So "**15 MeV electrons**" have exactly **15 MeV** just before passing through the window of the waveguide.

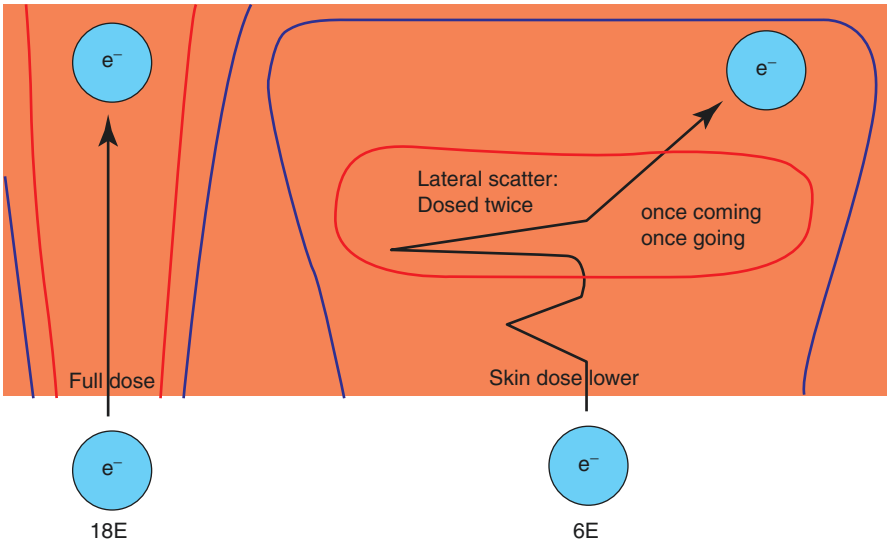
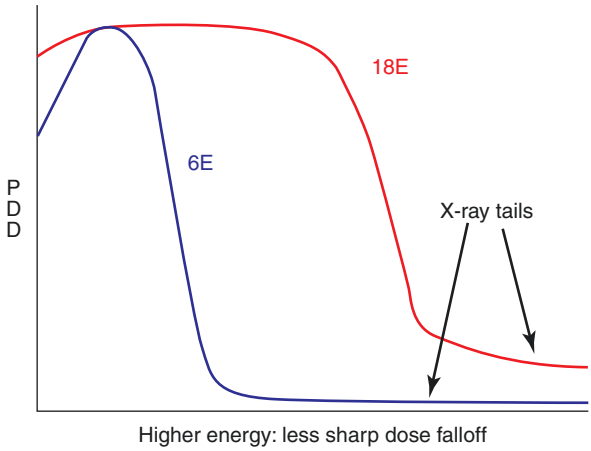


Fig. 10.3 Multiple scatter and depth dose. Scatter causes a dose buildup effect at a small depth (~1–2 cm) from the surface. Higher energy electrons scatter less, so surface dose increases with energy, unlike with photons

Fig. 10.4 Dose falloff from electrons. Higher electron energies have a longer range, but they suffer from a less sharp distal dose falloff and a larger Bremsstrahlung X-ray "tail"



- Electrons lose energy in the scattering foil, monitor chamber, and while traveling through air.
  - This causes "energy straggling," resulting in a poly-energetic spectrum (Fig. 10.5).
- **E = Nominal energy** (i.e., **15 MeV**).
- **E_0 = Mean energy at patient surface = 2.33 MeV * R_{50}** (by definition).

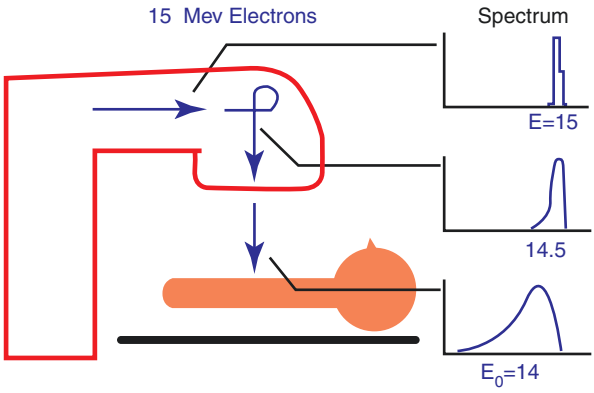


Fig. 10.5 Electron beam spectrum. Electrons exit the waveguide with a single well-defined energy, but their energy begins to "straggle" even inside the linac head. Electron energy at the patient's surface, E_0, is slightly lower than the nominal energy. Energy spectrum is shown at various locations

  - **E_0** is the primary measure of **beam quality** for electrons.
  - This number is always slightly less than the accelerator energy. **15-MeV** electrons may have an **E_0 = 14 MeV**.
- Within the patient (or phantom), mean electron energy decreases linearly with depth z, as described by **Harder's equation**:

$$E_Z = E_0 \times \left(1 - \frac{z}{R_p}\right) \tag{10.2}$$

- **Approximate electron range versus nominal energy (E)**:
  - **R_p** (practical range) ~ **=E/2 cm**
    This is a very reliable number.
  - **R_{80}** (range of 80% IDL) ~ **=E/2.8 cm**
    Different sources quote different numbers.
  - **R_{90}** (range of 90% IDL) ~ **=E/3.2 cm**
    Different sources quote different numbers.

Electrons: Isodose Shape and Energy Selection

- Electron isodose lines (IDLs) have a characteristic shape due to scatter (Fig. 10.6).
- Clinical energy selection should be based on target volume coverage by the X% isodose line.
  - **Example**: "9 MeV electrons prescribed to the 90% IDL."
- **If CTV coverage is not adequate**, there are two main ways to improve it:
  - Prescribe to a lower IDL:
    Drawback = hotter hot spot (**D_{max}**).
  - Select a higher electron energy:
    Drawback = longer range, more dose to deep normal tissues.

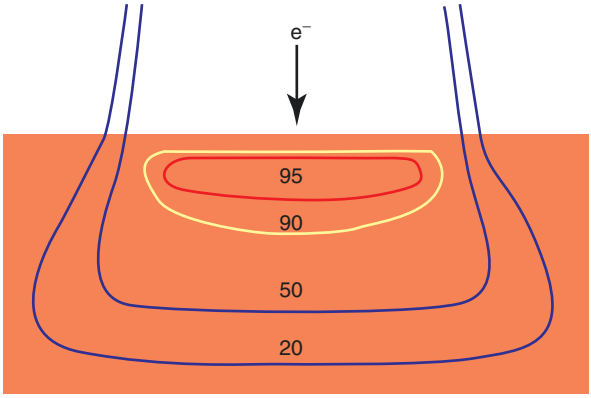


Fig. 10.6 Electron isodose lines. High isodose lines (95, 90%) "pull in" at depth, while low isodose lines (50, 20%) "bow out" at depth

Electron Field Shaping: Cones and Cutouts

- Electrons spread out as they pass through air. Therefore, **collimator jaws** are **useless** for setting electron field size.
- Electron applicators ("**cones**") extend from the linac head to very near the patient, decreasing the air gap.
  - Air gaps between **cone** and patient result in a poorly defined field edge (wide penumbra).
- The **electron output factor** (**K**) depends on the electron cone but should be 1.0 for a reference cone typically 10 cm.
  - Typically, field size is determined by **electron cone** size, not collimator jaw settings (the jaws are held in the same position).
  - If the collimator jaws change position, **K** will change dramatically due to **collimator scatter**.
- Custom blocks ("**cutouts**") should be thick enough to completely stop the electrons.
  - The closer the block is to the skin (less air gap), the sharper the field edge.
  - Although there is no forward scatter (the electrons are completely stopped), there is very high side-scatter and backscatter.

    If a block is touching the patient, it should be coated with wax to avoid overdosing the patient with backscatter electrons.

Electron Field Size Effects

- **Field size effects on output and PDD**:
  - If the field radius exceeds the practical electron range ($\mathbf{r} > \mathbf{R_p}$), it does not matter how big it is the dose remains nearly same.
  - The electrons from the edge of the field cannot reach the field center, and vice versa, so field size does not affect central axis dose.

- **This makes electrons very easy to calculate**:
  - **1MU = 1 cGy at d_{max}, 100 SSD**.
- **As the field size shrinks to < R_p**:
  - Some of your electrons escape out of the field, especially at depth.
  - **K** decreases: you need more beam to give the same dose.
  - **d_{max}** decreases: the dose becomes more superficial.
  - **PDD**s decrease with depth.
  - **Surface dose** increases.
  - **R_p** is unchanged because electron energy is unchanged.
- In a complex-shaped field, **any parts of the field narrower than R_p may be underdosed**.
  - Therefore, electron fields require more margin from CTV to block edge compared to photon fields.
    Approximately **2 cm** for electrons compared to **8 mm** for photons.
- SSD and effective SSD (aka virtual SSD) (Fig. 10.7).
  - Electron divergence can be extrapolated to a position known as the **effective** ("**virtual**") **source**.
- For **extended SSD**, the inverse-square factor must be calculated with **effective SSD** rather than true **SSD**.

$$\mathrm{ISF} = \left(\frac{\mathrm{SSD_{eff}}}{\mathrm{SSD_{eff}} + \Delta \mathrm{SSaD}} \right)^2 \tag{10.3}$$

- **ΔSSD** is the change in SSD you are trying to calculate.
- **Example**: Let's say that a 6 MV electron beam with a **true SSD** of **100 cm** has an **effective SSD** of **80 cm**.
  - What is the **ISF** at **SSD = 110 cm** (**ΔSSD** = 10 cm)?
    ISF = $(80/90)^2 = 0.790$

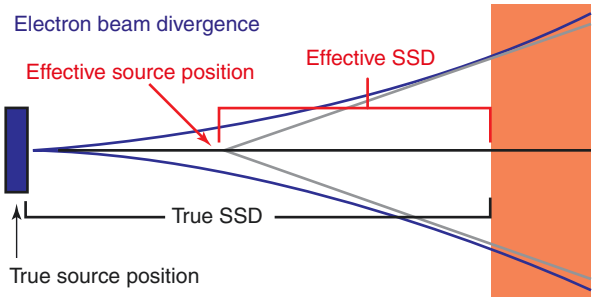


Fig. 10.7 Electron effective SSD. Because electrons are negatively charged, they repel each other as they travel through air. As a result, electron beams diverge more than they would based on geometry alone. They diverge as if they had a shorter SSD, which is known as the "effective SSD"

– What is the **ISF** at **SSD = 125 cm** (**ΔSSD** = 25 cm)?
ISF = $(80/105)^2 = 0.580$

Obliquity Effects

- Obliquity greatly alters electron dose distribution as shown in Fig. 10.8.
- **Decreased d_{max}** and **increased surface dose**:
  – This is the same effect as in photons but much stronger.
- **Increased dose at D_{max}**:
  – This is different from photons.
  – The **obliquity factor** (**OF**) is a measure of how much the dose increases with oblique angles.

$$\mathrm{OF}(\theta) = \frac{\text{Dose at oblique angle } \theta}{\text{Dose en face}} \tag{10.4}$$

- Loss of normal PDD curve:
  – Oblique angles decrease the depth dose but do not change the electron range (Fig. 10.9).
  – This is usually undesirable, and tangential electron fields are avoided in most standard treatments. However, they are desirable for total skin electron therapy.

Electron Field Matching

- **Electron–electron match**:
  – Both electron fields will bow into each other and cause severe hot spots. **Avoid if possible**.
- **Electron–photon match** (Fig. 10.10).

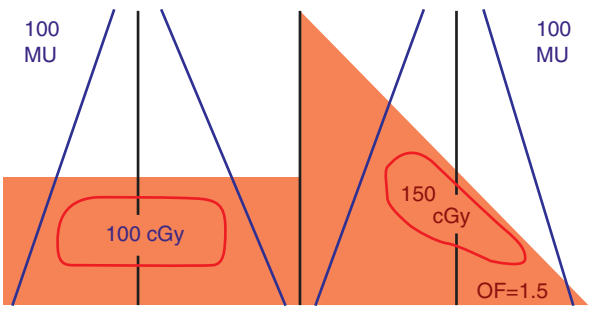


Fig. 10.8 Electron obliquity effects. Unlike photons, electrons deliver much higher dose to oblique surfaces than to flat ones

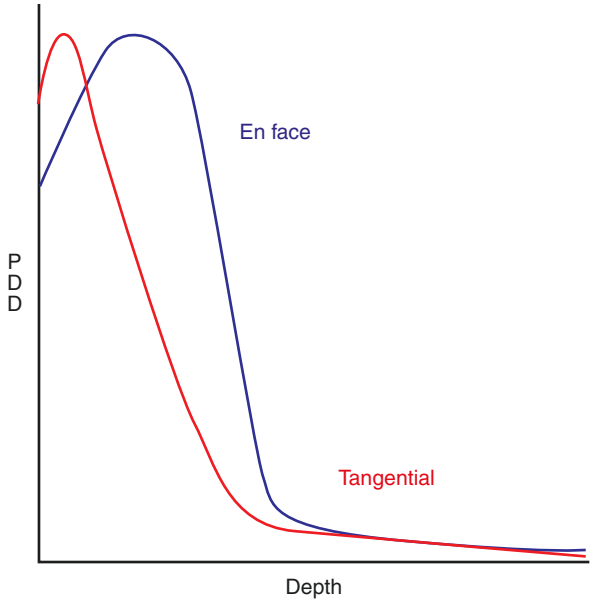


Fig. 10.9 Electron tangent PDD curve. High obliquity results in a loss of the steep distal falloff. Instead, dose falloff starts at a shallow depth and continues all the way to R_p

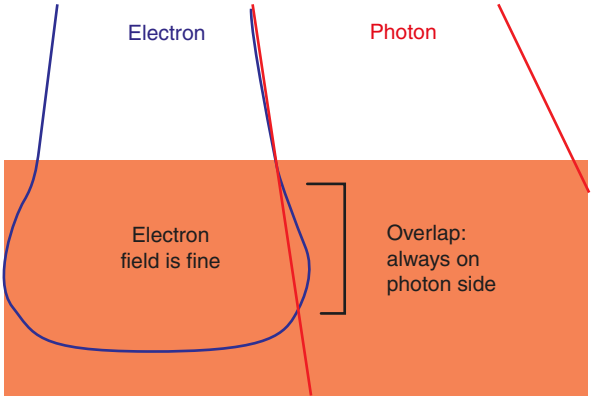


Fig. 10.10 Electron–photon match. When two fields are directly juxtaposed, electrons will "bow in" to the photons and cause a hot spot on the photon side

- A skin gap may be used to limit this hot spot.
  No easy equation – use treatment planning system.
  Like all skin gaps, this results in a superficial cold spot.
- Gantry rotation may also be used to limit this hot spot.
  Can rotate the electron field away from the photon field, or vice versa.
  This also results in a superficial cold spot.

Electrons and Inhomogeneities

- Range of electrons is determined by **electron density** (roughly proportional to mass density, **H**ounsfield **U**nits).
  - Electrons have a shorter range in high-density tissue and a longer range in low-density tissue.
- **Coefficient of equivalent thickness** (**CET**) = roughly equal to electron density.
- **Equivalent thickness = thickness** * **CET**.
  - **CET**(lung) = 0.25.
    1 cm of lung will have the same effect on an electron beam as 0.25 cm of water.
  - **CET**(bone) = 1.6.
    1 cm of bone will have the same effect on an electron beam as 1.6 cm of water.
- **Edge effects**: due to differential **scatter** (Fig. 10.11).
  - "**Electrons take the path of least resistance**": this rule of thumb states that the hot spot always occurs in the lower density medium.
    When tissue abuts metal, tissue is overdosed.
    When tissue abuts air, the air is overdosed and tissue may be underdosed.
  - Beware of electron inhomogeneity effects around air cavities. This may be pronounced in head and neck plans.

Bolus

- Just like with photons, bolus increases surface dose.
- However, bolus also decreases the range of electrons.
  - **Example**: 12 MeV electrons have an 80% IDL at 4 cm. With 0.5 cm bolus, the 80% IDL is at 3.5 cm.

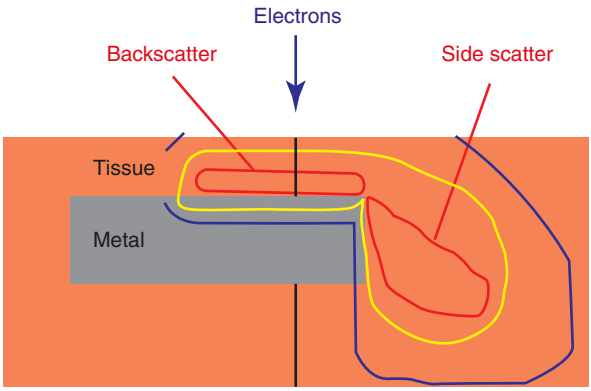


Fig. 10.11 Electron edge effects. A high-density structure such as metal will cause severe scatter in an electron field. Backscatter results in a proximal hot spot, and side-scatter results in a "rabbit ear" shaped hot spot

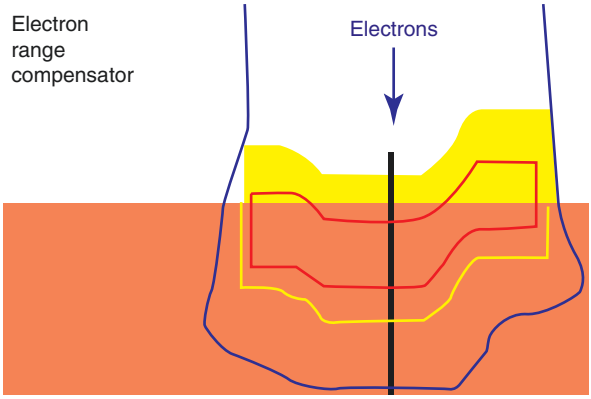


Fig. 10.12 Electron range compensator. Placing bolus material in an electron field not only changes the depth dose but also changes the range in tissue. This may be used to shape the distal edge of the radiation field

- Irregular shaped bolus may be used to smooth out obliquities and irregular patient contours.
- Irregular shaped bolus may also be used as a "range compensator" as shown in Fig. 10.12.

Beam Spoilers

- A beam spoiler degrades the energy (range) of electrons.
  - This pulls in the isodose lines just like adding bolus.
- It also adds some surface dose, but less than bolus (because it is not actually touching the patient).

Electron Arcs

- Sometimes used for chestwall irradiation.
- Very complicated to calculate.
- Most important feature is the **characteristic angle** (**β**). This determines the PDD and amount of photon contamination (Fig. 10.13).
- **Larger β** = less photon contamination = **better**.
- **Smaller β** = more photon contamination = **worse**.
- Blocking (cutouts) may be placed on skin.
  - Arc is started and stopped **past** the blocks to ensure a uniform dose.

Total Skin Electron Irradiation (TSEI)

- **Many different techniques exist for TSEI**.
- **Extended SSD** with matched upper and lower fields.

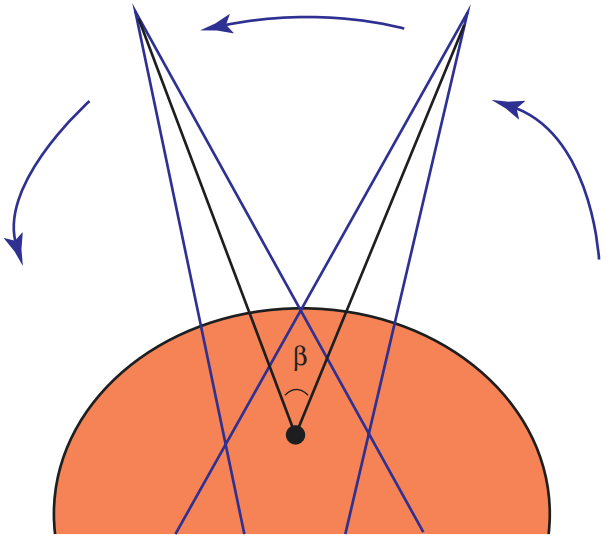


Fig. 10.13 Electron arc irradiation. The characteristic angle β is defined by the amount of arc rotation required to make two directly abutting but nonoverlapping fields. Larger values of β are desirable

  - Pointing beam up or down minimizes photon dose, as central axis is away from midline.
- **Multiple body positions** (at least 6) to ensure uniform skin coverage.
  - **1 cycle = 6–12 fields = ~300 cGy**.
  - **2–3 fractions/cycle**.
  - **1–2 cycles/week**.
- **Beam spoiler**: degrades energy, so less penetration into deep tissues. Also generates scatter to increase skin dose.
- Use patient dosimetry (**diodes**, etc.) for skin folds (groins, buttocks, etc.) and scalp.
  - May need to boost any areas that are underdosed.
- May use lead shielding as needed (eyes, fingernails, etc.).

Rules of Thumb

- **Electron fields are easy to calculate**:
  - **1 MU = 1 cGy at the 100% isodose line (d_{max}) for standard jaw settings, large field size**, and **no obliquity**.
  - For small field size, **output factor** (**K**) should be measured.
- **For electrons of nominal energy = E MeV**:
  - **R_p** (practical range) ~ **=E/2 cm**
  - **R_{80}** (range of 80% IDL) ~ = **E/2.8 cm**
  - **R_{90}** (range of 90% IDL) ~ = **E/3.2 cm**

- **Surface dose increases with energy**:
  - **~70–80**% at **6 MeV**
  - **95**% at **18 MeV**
- **Effective** (**virtual**) **SSD is shorter than true SSD**.
  - Inverse-square factor should use effective SSD.
- "**Electrons bow into photons**."
  - The hot spot is always on the photon side of match.
- "**Electrons take the path of least resistance**."
  - At a density interface (such as metal next to tissue), a hot spot will appear in the lower density structure.
- **Obliquity** = hot spot near surface (**obliquity factor**), higher surface dose, and less sharp distal falloff.
  - Avoid tangential electron fields.

Physics and Dosimetry of Brachytherapy

11

Introduction

Unlike teletherapy, brachytherapy involve treatment with radioisotopes. Radium brachytherapy is the oldest form of radiation therapy. In the modern era, many different nuclides and devices are used for brachytherapy. The properties of a sealed source vary with encapsulation. Source strength is specified by activity as well as air kerma strength. Dose calculations are based on a formula that incorporates geometry factor, anisotropy factor, and radial dose function.

Definitions

- **AAPM TG-43**: Task Group Report of the American Association for Physics in Medicine (AAPM) for brachtherapy dosimetry.
- **Activity** (**A**): Amount of radioactive material.
  - Units: 1 Curie (**Ci**) = 3.7×10^{10} Becquerel (**Bq**).
- **Radius** (**r**): aka distance, depth.
- **Dose rate** ($\dot{D}$): not to be confused with total dose (**D**).
- **Initial dose rate** ($\dot{D}^0$).
- **Exposure rate constant** (**Γ**), aka **gamma constant**: Exposure rate per millicurie of isotope at 1 cm distance.
- **Exposure rate** ($\dot{X}$) = **ΓA**.
- **Milligrams radium equivalent** (mgRaEq):
  - **1 mgRaEq = 8.25 R-cm^2 -h $^{-1}$ -mg $^{-1}$ exposure rate**
- **Air kerma strength** (S_K): Kerma (kinetic energy released in matter) measured in air @ 1 m.
  - **1 U = 1 cGy-cm $^{-2}$ -h $^{-1}$ = 1 μGy-m $^{-2}$ -h $^{-1}$**
  - Proportional to **activity but modern way to represent**.

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- **Dose rate constant** (**Λ**): Dose rate in water for 1 U air kerma strength at 1 cm (cGy-cm^{-2}-h^{-1}/U).
- **Low-dose rate** (**LDR**): **0.4–2 Gy/h**.
- **Medium-dose rate** (**MDR**): **2–12 Gy/h**.
- **High-dose rate** (**HDR**): **>12 Gy/h**.
- **Pulse dose rate** (**PDR**): HDR fractionated over time to approximate LDR dose rates.
- Details of the units and activities along with dosimetry can be found in **AAPM TG-43 and its update**.

The Historical Role of Radium

- **^{226}Ra** brachytherapy was used for many decades (till 1990) prior to ^{60}Co, ^{137}Cs, ^{192}Ir, or megavoltage X-rays.
- **Radium sources** consist of radium chloride powder placed within a double-sealed platinum tube.
- **^{226}Ra** comes to a **secular equilibrium (see Chap. 2)** with **^{222}Rn** and its decay products by emitting alpha rays.
  - This results in accumulation of multiple radioactive daughter nuclides emitting alphas, betas, and gammas.
  - The encapsulation is designed to absorb everything except for the gammas. Average photon energy of ^{226}Ra is **0.83 MeV** (range 0.18–2.29 MeV).
- **^{226}Ra** is no longer used because of the risk of radon gas leakage and other safety concerns.
- Many LDR brachytherapy systems are based on "milligrams radium equivalent" (**mgRaEq**).
  - For a source of activity A and gamma constant Γ:

$$\text{Radium Equivalent } (\text{mCi}) = \frac{\Gamma A \times \text{mg} \times \text{Ra} \times \text{Eq}}{8.25\ R/\text{cm}^2/\text{hr}} \tag{11.1}$$

Commonly Used Therapeutic Radionuclides

- Common sealed source nuclides include **^{226}Ra**, **^{192}Ir**, **^{137}Cs**, **^{125}I**, **^{103}Pd**, and **^{60}Co**.
- Common unsealed sources include **^{131}I**, **^{90}Y**, and **^{32}P**.
- Nuclides are chosen for their desired characteristics such as type of radiation, half-life, energy, and so on.
  - **^{125}I** and **^{103}Pd** emit very low-energy characteristic X-rays (22–28 keV) produced by electron capture (Chap. 2); this gives them a very steep dose falloff.
  - The other sealed source nuclides are high-energy gamma emitters.
  - Most unsealed source nuclides emit short-range beta radiation with a short half-life, thus limiting the risk of systemic and environmental contamination.
- Refer to **Appendix B** for a list of nuclides used in imaging and therapy.

Production of Radionuclides

- **Naturally occurring**: By-products of uranium decay, these nuclides can be mined from the Earth.
  - **^{226}Ra**, **^{223}Ra**, and **^{222}Rn**, among others.
- **Fission by-product**: Obtained from nuclear reactors.
  - **^{137}Cs**, **^{131}I**, and **^{90}Sr**, among others.
- **Neutron bombardment**: Creates beta-minus emitters. Cyclotrons can produce high-intensity proton and neutron flux. Nuclear reactors can produce very high-intensity neutron flux.
  - **^{198}Au**, **^{192}Ir**, **^{153}Sm**, **^{125}I**, **^{103}Pd**, **^{89}Sr**, **^{60}Co**, and **^{32}P**, among others.
- **Proton bombardment**: Creates beta-plus emitters, often used for PET imaging. Protons are accelerated by a cyclotron.
  - **^{123}I**, **^{68}Ga**, **^{18}F**, **^{15}O**, **^{11}C**, and **^{3}H**, among others.
- **Daughter elution**: A longer-lived mother nuclide ("cow") decays into a shorter-lived daughter nuclide ("milk") that can be repeatedly eluted for clinical use. This is an example of transient equilibrium.
  - **^{90}Y** and **^{99m}Tc**, among others.

Sealed Source Properties

- Classically, source strength is measured as activity (Ci or Bq) or milligrams radium equivalent (mgRaEq).
  - Two sources with the same **activity** (**Ci**) may emit very different amounts, energies, and types of radiation due to **encapsulation** and **filtration**. Hence, their dose rate may be different.
- Source strength is specified as air kerma rate at a distance of 1 m as mentioned above (**1 U = 1 μGy/h/m^2**).

Unsealed Source Properties

- Unsealed sources do not have to worry about encapsulation, so they simply are specified as **nuclide**, **activity**, and **chemical formulation** (i.e., elemental vs. colloidal vs. antibody-bound).
- An unsealed source will have separate **physical** and **biological** half-lives.
  - **Effective half-life equation**:

$$t_{\text{eff}} = \frac{\left(t_{\text{biol}} \times t_{\text{phys}}\right)}{\left(t_{\text{biol}} + t_{\text{phys}}\right)} \tag{11.2}$$

- See Chap. 2 for more half-life equations.

Implant Instrumentation and Technique (ICRU-38 and 58)

- An **intracavitary implant** is placed within an **applicator** such that the sources do not directly contact tissue.
  - Tandem and ovoids (i.e., Fletcher-Suit)
  - Ring and tandem
  - Vaginal cylinder
  - Partial breast balloon brachytherapy
  - Endobronchial
- An **interstitial implant** is inserted into tissue.
  - Template-based catheters
  - Free-hand catheters
  - Permanent seeds
- **Other** types.
  - Surface applicator (eye plaque, intraoral, skin)
  - Intravascular
  - Intraoperative
- **Unsealed sources** may be given systemically (oral, intravenous) or injected in a specific location (intracystic, intra-articular).

Brachytherapy Dose Rate

- **LDR** implants deliver dose over days (temporary) to months (permanent).
  - Temporary LDR implants: Typical dose rates are approx. **~60 cGy/h** or 1 cGy/min.

    Permanent implant dose rates are much lower, but total dose is very high such as in prostate seed implants (120–145 Gy).
  - Normal tissue sparing effect due to sublethal damage repair (SLDR), see Chap. 29 for radiobiology details.
- **HDR** implants typically deliver dose over a few minutes, with typical dose rates **>50 cGy/min** (>3000 cGy/h).
  - Like external beam RT, fractions are given over a time scale shorter than that of DNA repair.
  - Computer-controlled **HDR** afterloaders allow for detailed optimization of dwell positions and times.

    Geometric normal tissue sparing is used to make up for loss of biological normal tissue sparing.
- **PDR** is a method that uses an **HDR** afterloader to deliver fractions every hour or so, to approximate **LDR** dose rates.

Permanent Implants: Decay Equations

- Dose is delivered over the entire life of the isotope, so activity will decay with time:

$$\text{Activity}: A(t) = A_0 e^{-\lambda t} \tag{11.3}$$

$$\text{Half}-\text{Life}: t_{1/2} = \frac{0.693}{\lambda} \tag{11.4}$$

$$\text{Mean Life}: = \frac{1}{\lambda} = 1.44 \times t_{1/2} \tag{11.5}$$

- Since dose rate is proportional to activity:

$$\text{Dose Rate}: \dot{D}(t) = \dot{D}_0 e^{-\lambda t} \tag{11.6}$$

- Total dose is equal to dose rate * mean life:

$$\text{Total Dose}: D = \dot{D}_0 \tau = 1.44 \times \dot{D}_0 \times t_{1/2} \tag{11.7}$$

Beta Emitter: Simple Dose Calculation

- If a beta emitter is evenly distributed in a mass of tissue and never leaves the tissue, dose can be calculated very easily:
  - Average beta energy $\bar{E}$ = max beta energy/3
  - **1 eV = 1.6 × 10^{-19} J**
  - **M** = mass of tissue
  - **1 Gy = 1 J/ kg**

$$\begin{aligned} \text{Dose Rate}: \dot{D}\ (\text{Gy/s}) &= \frac{A\ (\text{Bq}) \times \bar{E}\ (\text{J})}{M\ (\text{kg})} \\ \text{Total Dose}: D &= \dot{D}_0 \tau = 1.44 \times \dot{D}_0 \times t_{1/2}\ (\text{s}) \end{aligned} \tag{11.8}$$

Photon Emitters in Air: Exposure and Dose Rate

$$\text{Exposure Rate}\left(\text{air}\right): \dot{X} = \frac{\Gamma \times A}{r^2} \tag{11.9}$$

- Gamma (Γ) is called the **exposure rate constant** for a good reason, and it can directly calculate exposure rate in air.

$$\text{Dose Rate}\left(\text{air}\right): \dot{D} = f \times \dot{X} \tag{11.10}$$

- f = f-factor (cGy per R conversion factor) (see Chap. 6).

Photon Emitters in Water: Γ Based Dose Claculation

- Assume an isotropic (equal in all directions) dose distribution.

$$\dot{D}\left(r\right) = \frac{f \times \Gamma \times Aa \times \left(r\right)}{r^2} \tag{11.11}$$

  - Gamma (**Γ**) measures exposure rate in air
  - **a**(**r**) = attenuation function
    This accounts for photon attenuation by the medium.
    This is very similar to the radial dose function, **g**(**r**). See section below.

Photon Emitters in Water: TG-43 Dose Claculation: Radial Dose Function (*g*)

- Accounts for the shape and attenuation of the source.

$$\dot{D}\left(r,\theta\right) = S_k \times \Lambda \times \frac{G\left(r,\theta\right)}{G\left(1,\pi/2\right)} \times F\left(r,\theta\right) \times g\left(r\right) \tag{11.12}$$

  - $\mathbf{S_k}$ = Air kerma rate
  - **Λ** = Lambda (dose rate) constant
    Converts kerma in air to dose in water.
  - **G**(**r**,**θ**) = Geometry factor

Modified inverse-square equation that accounts for the linear shape of the source.

- **F(r,θ)** = Anisotropy factor
  Accounts for attenuation within the source.
- **g(r,θ)** = Radial dose function
  Accounts for attenuation and scatter within the medium (water).

TG-43 Dose Claculation: Geometry Factor (*G*)

- **G(r,θ)** is known as the **geometry factor** and defines the inverse-square dose falloff with distance (Fig. 11.1).
- For a point source, $\mathbf{G(r) = 1/r^2}$ (inverse square).
- For a line source, $\mathbf{G(r,\theta) = (\theta_2 - \theta_1)/Ly}$.
  - This is an integral of the inverse-square distance to every point on a line.
  - For distances much larger than the source length, **G(r,θ)** will approximately equal $\mathbf{1/r^2}$.

TG-43 Dose Calculation: Anisotropy Factor (F)

- All sources have some degree of **anisotropy**. This means that the dose varies with angle to the source (Fig. 11.2).
- This is because of differential **attenuation** from the source encapsulation (Fig. 11.3).
  - **F**(*r, θ*) is defined as 1.0 at perpendicular angles ($\mathbf{\theta = \pi/2}$), and its value changes as you move off-axis.
    This is analogous to an **OAR** for external beam (see Chap. 8).

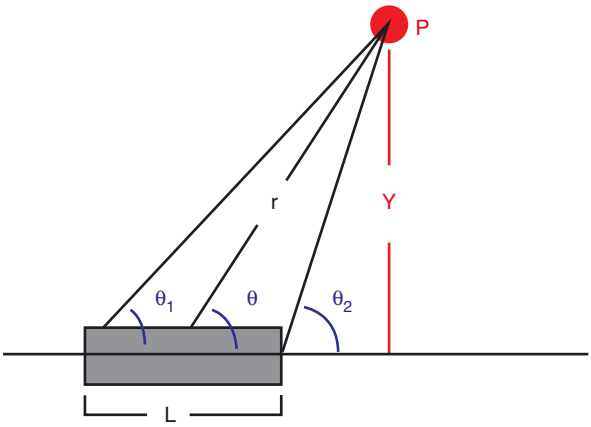

Fig. 11.1 Geometry factor (*G*) which is a function that calculates the inverse-square falloff of a line source. For a point source, G is equal to the inverse-square factor

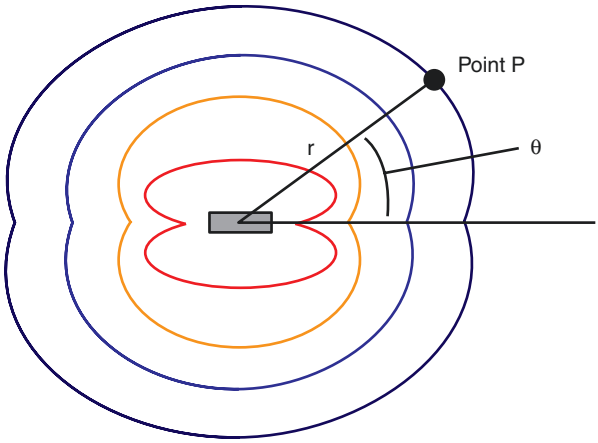

Fig. 11.2 Anisotropy factor (F). This correction factor compensates for variation in attenuation with the angle to the source

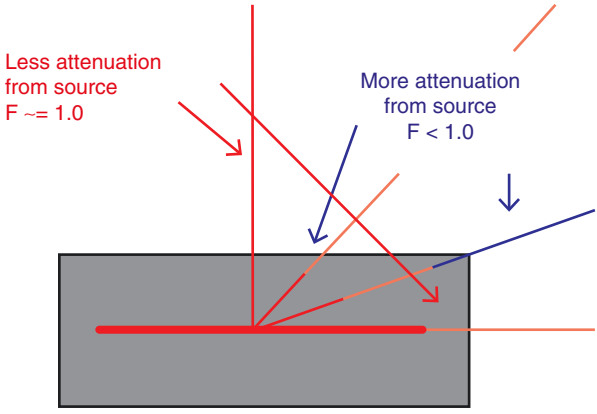

Fig. 11.3 Differential attenuation. Due to the cylindrical shape of a sealed source, radiation exiting the source at an oblique angle must pass through more encapsulation, thus self-attenuation and lower dose

TG-43 Dose Calculation: Radial Dose Function (*g*)

- **g(r)** is the **radial dose function** and describes the change in radial dose falloff when measured in water instead of air.
  - This is analogous to a **TAR** for external beam (see Chap. 8).
  - **Scatter** increases depth dose.
  - **Attenuation** decreases depth dose (Fig. 11.4).
  - For high-energy gamma sources: Scatter and attenuation roughly cancel out over short distances (r < 5 cm):
    g(r) ≈ 1. Dose falloff in water is very similar to dose falloff in air.
  - For low-energy X-ray sources (^{125}**I**, ^{103}**Pd**) attenuation dominates over scatter.
    g(r) < <1. Dose falls off much more rapidly in water than in air.

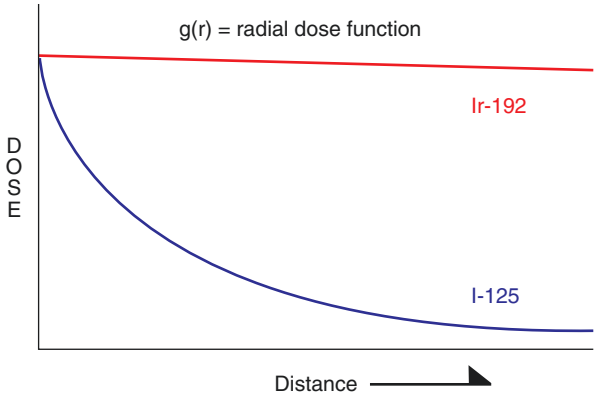

Fig. 11.4 Radial dose function (g) and type of sealed source. This function compensates for the difference between dose to air and dose to water. Low-energy sources fall off very rapidly with distance, while high-energy sources do not

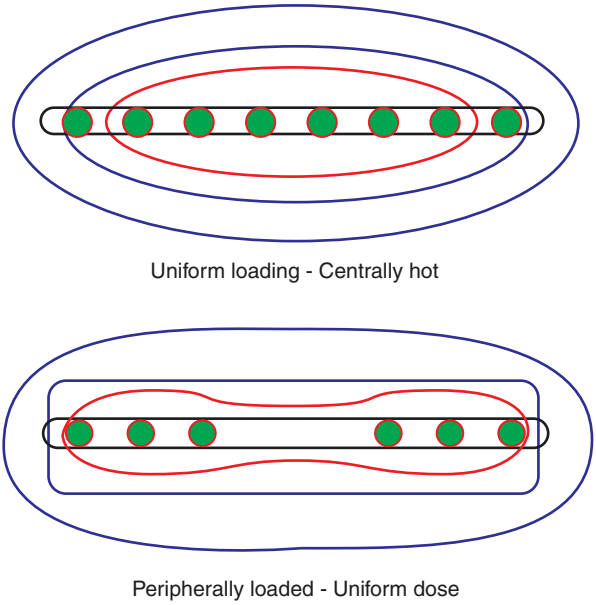

Fig. 11.5 Brachytherapy loading principles. A uniformly loaded catheter will always give a higher dose to the center. This effect may be countered with peripheral loading

Loading Patterns: Basic Principles (Fig. 11.5)

- In a uniformly loaded catheter, the center will receive more dose than the ends.
- Therefore, if you want a homogenous dose, you need **peripheral loading**—more source strength at the ends.
- This is true for both **LDR** and **HDR**.

Classical Dose Systems (Interstitial)

- Prior to computer planning era, precalculated tables were used to calculate how much radium was needed to load an implant. These are of mainly historical interest (Fig. 11.6).
- **Paterson-Parker** (**Manchester**):
  - Different dose-loading tables for single-plane, two-plane, and volume implants.
  - **Peripherally loaded** – nonuniform loading.
  - **Uniform dose** within implanted volume.
  - **Crossed ends** – needles/catheters run perpendicular to each other.
- **Quimby**
  - Different dose-loading tables for single-plane, two-plane, and volume implants.
  - **Uniform loading**.
  - **Central hot spot** within implanted volume.
  - **Crossed ends** – needles/catheters run perpendicular to each other.
- **Paris**
  - Volume implants with multiple parallel needles or catheters.
  - **Uniform loading**, identical for all needles.
  - **Uniform spacing** of all needles.
  - **Central hot spot** within implanted volume.
  - **Parallel ends** – no crossing of needles.
- **Other**
  - **Prostate** – computer planning is preferred over fixed systems.

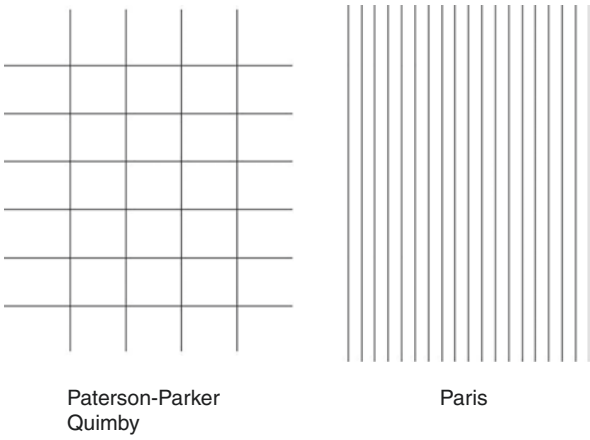

Fig. 11.6 Historical brachytherapy loading systems. The Paterson-Parker and Quimby systems utilize crossed ends, while the Paris system does not

Classical Dose Systems (Intracavitary)

- **Fletcher-Suit** (**named after Gilbert Fletcher and Herman Suit**) for cervical cancer treatment.
  - Dose is prescribed to **Point A**:
    2 cm superior to the top of the ovoids as seen on a lateral film.
    2 cm lateral to the tandem, in a direction perpendicular to the tandem as seen on an AP film.
    This is supposed to represent the **paracervical triangle** where the uterine vessels cross the ureter.
  - **Revised Point A** is 2 cm superior to the flange:
    Unlike classical Point A, this point can be visualized on AP film alone (no need for laterals).
    Point H is the prescription point used by the American Brachytherapy Society.
    - Find the intersection between the tandem and a line drawn between the mid-dwell positions of both ovoids.
    - Move cephalad along the tandem by 2 cm plus the radius of the ovoids.
    - Then, move lateral by 2 cm.
    - This is intended to be the same point as **classical Point A**, but with more reproducible delineation.

    However, it is a bit lower than **classical Point A**.
  - Typical **LDR** dose rate is 50–60 cGy/h to **Point A** (Fig. 11.7).
  - Additional dose measurements at:
    Point B is 3 cm lateral to **Point A** (5 cm from midline), which represents the **obturator nodes**.
    Point P is the bony pelvic sidewall, either at the level of **Point A** or at the top of the acetabulum.
    Bladder point is defined by the posterior extent of the bladder directly behind the Foley catheter.
    Vaginal point is defined by the posterior extent of the vaginal packing, at the level of the midpoint of both ovoids.
    Rectal point is defined as 5 mm posterior to the vaginal point.

Rules of Thumb

- **How do we specify source strength**?
  - **Activity** (**A**) [Ci, Bq]:
    Gamma constant (**Γ**) [R/cm^2/h] measures exposure in air per mCi.
    Exposure rate in air = AΓ.

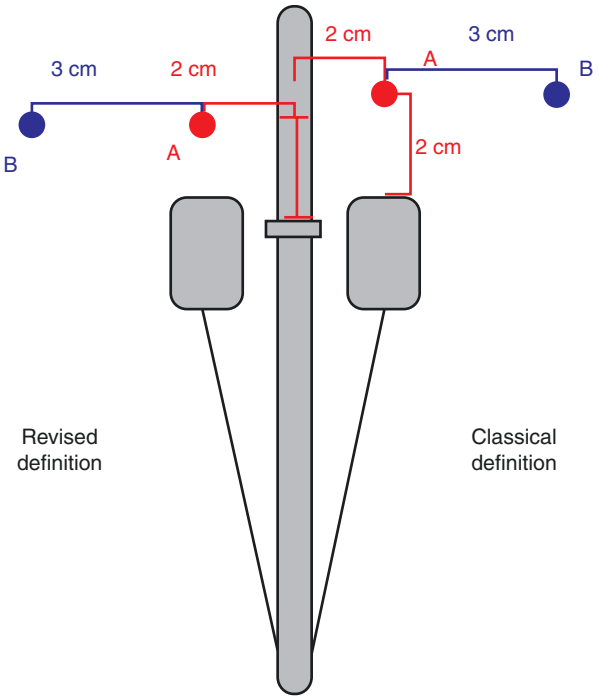

Fig. 11.7 Definitions of Point A. Point A is the typical prescription point for cervical brachytherapy. The original definition is 2 cm lateral to the tandem and 2 cm above the top of the ovoids. The revised definition is 2 cm lateral to the tandem and 2 cm above the top of the flange

  - **Air kerma strength, AKS** ($\mathbf{S_k}$) [cGy/cm²/h, U]:
    Lambda constant ($\mathbf{\Lambda}$) measures dose rate to water per unit of AKS.
    Dose rate in water = $\mathbf{S_k\Lambda}$.
- **Milligrams radium equivalent**:
  - A 1 mgRaEq source is a source with the same air exposure rate as 1 mg of radium:

$$\text{mg RaEq} = \frac{\Gamma A}{8.25\ R/\text{cm}^2/\text{hr}}$$

- **Effective half-life (unsealed source)**:

$$\mathbf{t}_{\text{eff}} = \frac{\left(t_{biol} \times t_{phys}\right)}{\left(t_{biol} + t_{phys}\right)}$$

  - Always shorter than biological or physical half-life.

- **Permanent implant equations**:

$$\text{Mean Life}: \tau = \frac{1}{\lambda} = 1.44 \times t_{1/2}$$

$$\text{Dose Rate}: \dot{D}(t) = \dot{D}_0 e^{-\lambda t}$$

$$\text{Total Dose}: D = \dot{D}_0 \tau = 1.44 \times \dot{D}_0 \times t_{1/2}$$

- **TG-43 Calculations**:

$$\dot{D}(\mathrm{r},\theta) = S_k \times \Lambda \times \frac{G(r,\theta)}{G(1,\pi/2)} \times F(r,\theta) \times g(r)$$

  - $\mathbf{S_k}$ = Air kerma strength.
  - $\mathbf{\Lambda}$ = Dose rate factor (lambda constant).
  - **G** = Geometry factor (analogous to inverse-square factor).
  - **F** = Anisotropy factor (analogous to off-axis ratio).
  - **g** = Radial dose function (analogous to **TAR**).
- **Dose falloff**:
  - Inverse square is almost always a larger factor than tissue attenuation (**G** falls off faster than **g**).
  - High-energy sources (Not ^{125}I or ^{103}Pd): Attenuation and scatter approximately cancel out ($\mathbf{g} \approx \mathbf{1}$).
- **Uniform loading = Central hot dose**.
- **Peripheral loading = Uniform dose**.
- **Classical brachytherapy systems**:
  - **Paterson-Parker**: Crossed needles, **p**eri**p**heral loaded, uniform dose.
  - **Quimby**: Crossed needles, uniform loaded, **qu**ite hot in the center.
  - **Paris**: **Par**allel needles (not crossed), centrally hot.
  - **Fletcher-Suit**: Intracavitary implant, classical Point A is higher than revised Point A.

    Classical definition requires heavier loading (more activity) for the same "Dose to Point A."

Advanced Treatment Planning for EBRT

12

Introduction

Treatment planning techniques include patient immobilization, imaging, radiation field design, verification, and evaluation. Modern radiotherapy takes advantage of many different imaging modalities, including traditional radiography, computed tomography (CT), magnetic resonance (MR), positron emission tomography (PET), and ultrasound (US). Once target and avoidance volumes are defined, radiation fields may be planned using 2D, 3D, or intensity-modulated radiotherapy (IMRT) techniques and evaluated using dose-volume histograms (DVHs). Additional imaging may be performed on the day of treatment to verify that the patient is properly positioned.

What Is Advanced Treatment Planning?

- This chapter focuses on advanced treatment planning techniques:
  - Imaging techniques
  - Immobilization techniques
  - Treatment planning and evaluation techniques
- See Chap. 9 for details on basic treatment planning:
  - Irregular surface compensation
  - Wedges
  - Bolus
  - Field matching (gap calculation)
  - International commission of radiation units and measurements (ICRU) reference dose definition

2D Radiography

- **Plain film** must be selected based on:

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  - **Energy** (kV film is very different from MV film).
  - **Sensitivity** (is it a 2 cGy port film, or a 200 cGy whole-fraction verification?).
- **Electronic imaging** is performed by:
  - Fluoroscopy: conversion of X-rays to visible light.
  - Ionization chamber array: limited resolution.
  - Amorphous silicon panel: most modern technology.
- **Real-time imaging** may be performed with fluoroscopy or by setting a digital flat-panel to "fluoro" mode.
- Diagnostic-energy **radiographs** are characterized by:
  - Kilovolts peak (**kVp**): maximum X-ray energy. Increasing **kVp** increases **exposure** and **penetration** but decreases **contrast**.
  - Milliamp-seconds (**mAs**): product of tube current and time. Increasing **mAs** increases **exposure** only.
  - **Magnification**: image on film is always larger than true size, because of beam divergence.

$$\text{Magnification} = \frac{\text{FFD}}{\text{FAD}} \tag{12.1}$$

- **FFD** = Focus-film distance
- **FAD** = Focus-axis distance

Computed Tomography (CT)

- Measures in **Hounsfield units** (**HU**) and can be converted to **electron density** for treatment planning.
  - Air = −1000 HU, Water = 0 HU, Bone ≈ 1800 HU.
  - Electron density is required for dose calculation.
- Limited **bore size** and **field of view** (**FoV**) (Fig. 12.1).
- Finite **slice thickness** (typically ranges from 1 to 5 mm).

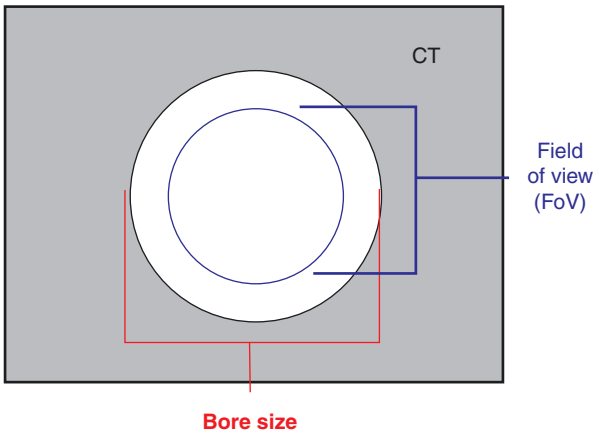

Fig. 12.1 CT bore size and FoV. The field of view is always significantly smaller than the bore size, so if a patient barely fits into a machine, you will not obtain an accurate image of the patients

- Only images the **axial** plane – sagittal and coronal planes are digitally reconstructed and less accurate.
  - High resolution in the axial plane.
  - Low resolution in the craniocaudal direction.
- Susceptible to **metal artifact**.
- Susceptible to **motion artifact**, unless **4DCT** is used.

Cone Beam CT (CBCT)

- Obtained using rotation of a 2D imager.
- Unlike regular CT, CBCT has equal resolution in all directions. Compared to regular CT:
  - **Lower** resolution in axial plane.
  - **Higher** resolution in craniocaudal plane.
- If the desired FoV is smaller than the imaging panel, it can operate in **whole fan** mode.
  - CBCT images the entire field at all times.
  - Requires a 180° rotation minimum.
- If desired FoV is larger than the imaging panel, can operate in **half fan** mode to double the FoV:
  - Half of the field is imaged at any given time.
  - Requires a 360° rotation minimum (Fig. 12.2).

Digital Tomosynthesis

- Uses the same principle as **CBCT** but attempts to synthesize a 3D image with less than 180° of rotation.
  - The larger the angle of rotation, the more accurate the image (at 180+ degrees, it becomes a **CBCT**).

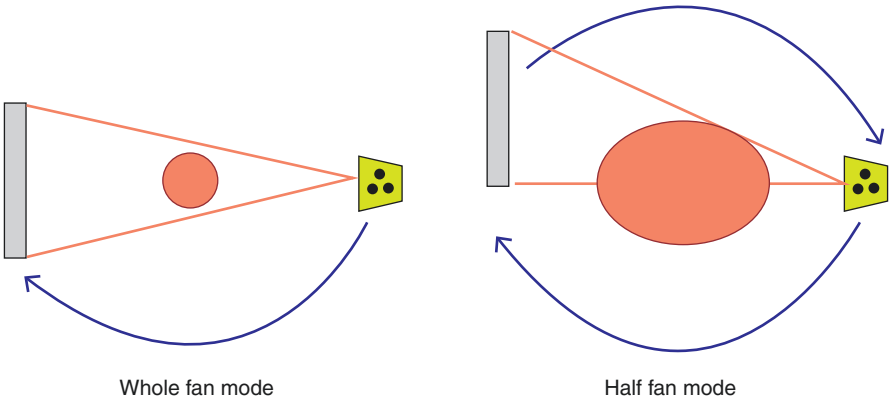

Fig. 12.2 CBCT fan modes. Whole fan mode is used to image small fields, while half fan mode is used to image large fields

  - Smaller rotational angles cause more artifacts.
- **Tomosynthesis** is used to obtain **CT**-like images with shorter imaging time and less imaging dose. It is used commonly in diagnostic radiology but less so in radiation oncology.

Magnetic Resonance Imaging (MRI)

- Measures **proton spin** using magnetic and radiofrequency fields. Please read more in Chap. 17 of this book.
  - Does **not** give direct electron density information.
- Not limited to the axial plane; can take true sagittal and coronal images.
  - **True 3D** sequences have equal resolution in all planes. Ideal for image fusion.
- **T1**: water dark, fat bright. Brain is "right side up" (white matter white, gray matter gray).
- **T2**: water bright, fat dark. Brain is "upside down" (white matter gray, gray matter white).
- **T2FLAIR**: water dark, fat dark. Brain is "upside down."
- **Other**: many, many different MR imaging sequence modalities depdending on design and manufacturer.
- Very limited **FoV**, different MR coil for each part of the body.
- Much worse **metal artifact** (even for MR-safe metals).
- Much worse **motion artifact**.
  - Due to long scan times, patient has more time to move.

Image Resolution

- Plain film and electronic film have sub-mm resolution, equal in all directions.
- Fluoroscopy generally has lower resolution than static film.
- **CT** has very high resolution in the axial plane, but much lower resolution craniocaudal.
  - Axial resolution = mm or sub-mm.
  - Craniocaudal resolution = slice thickness, which is usually several mm.
- **MRI** has good resolution and is capable of producing **3D** sequences with equal resolution in all planes.
  - However, **MR** images are limited by motion artifact.

Windowing and Leveling

- **CT** and **MR** data have a very broad range of intensities.
  - If the full range was displayed on screen, it would look "washed out."
- **Window** and **Level** allow one to select a range of intensities to display on screen.
- **Level** = the center of the intensity range.
  - **Example**: a CT with **L = 50** will display **HU = 50** as the average "gray" color.

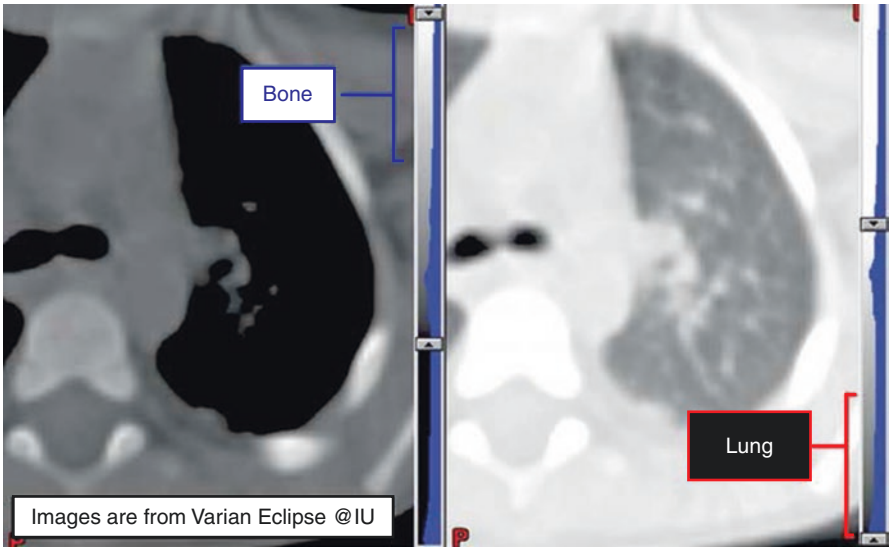

Fig. 12.3 CT windows. The same CT data set can be displayed in very different ways. This example shows bone windows versus lung windows. By scrolling panel on right, one can change window and level

- **Window** = the width of the intensity range.
  - **Example**: the same CT with **W = 100** will display **HU** values between (**0–100**) as a grayscale.
    HU < 0 will be completely black.
    HU > 100 will be completely white (Fig. 12.3).

Additional Imaging Modalities

- **Ultrasound** (**US**):
  - Measures **echo** of high-frequency sound waves.
  - Generates 2D images, often in real time.
  - **Doppler** may be used to image blood flow.
  - Transducer must be placed within a few cm of the structure being imaged.
  - Sound transmission is blocked by **density interfaces** (tissue/air or tissue/bone), limiting the anatomic sites that can be imaged.
  - Often used for brachytherapy (intraoperative imaging), prostate localization and cavity in breast.
- **Nuclear isotope imaging**:
  - In general, this allows the imaging of biological uptake but has lower resolution compared to CT or film.
  - **^{18}FDG-PET** uses **^{18}F**, a positron emitter.
    Images sugar (glucose) uptake.
    Positron annihilation results in pairs of 511 keV photons, detected by a specialized **coincidence detector**.

  - **Other PET** uses different isotopes and tracer molecules.
    Na ^{18}F PET images blastic and lytic bone lesions.
    ^{11}C Acetate PET images ketone body uptake.
    Other PET isotopes are currently experimental.
  - **^{99m}Tc MDP bone scan**: images blastic bone lesions.
  - **^{99m}Tc sestamibi**: images myocardial perfusion.
  - **^{99m}Tc MAG3**: images renal perfusion.
  - **^{99m}Tc sulfur colloid**: radioactive blue dye used for sentinel node biopsy.
  - **^{123}I iodine scan**: used for imaging (not treatment) of thyroid carcinomas.
  - **^{131}I iodine scan**: used for treatment of thyroid carcinoma and can also be imaged.

Patient Setup Considerations

- Must be comfortable enough to hold position for simulation and treatment.
- Must be easily reproducible day to day. Highly mobile body parts such as head and extremities may require immobilization devices.
- Patient setup considerations:
  - Supine versus prone versus more exotic positions.
  - Dentures, obturators, and other prosthetics: leave them on or take them off?
  - What degree of immobilization is desired? What devices are desired?
  - What bolus is desired? Does a custom bolus need to be created?
  - Will skin folds create an undesirable "self-bolus" effect?
  - Will the patient + devices fit into the CT field of view?
  - Will the shoulders or arms interfere with the beam?
  - Will the shoulders or arms interfere with the treatment machine (such as electron cone–shoulder collisions)?

Advanced Immobilization Devices

- Stereotactic radiation treatments (**SRS**, **SBRT**, **SABR**) require very high precision to provide accurate dose to target and avoid overdosing normal tissue.
  - Immobilization devices are very important.
- **Cranial immobilization**:
  - **Invasive head frames** pierce the skin and attach to the skull.
  - **Noninvasive head frames** do not pierce the skin. They use bite blocks ± other features (ear buds, etc.).
  - **Frameless devices** use Aquaplast ± bite block.
- **Extracranial immobilization**:
  - **Stereotactic body frames** encompass the torso with some form of rigid registration.
    Internal fiducials that can be imaged.
    Indexed frames attach to the couch in a well-defined position.

  - **Other body molds** such as Alpha Cradle and HipFix.
  - **Rectal balloons** for prostate.
  - **Respiratory management**:
    Abdominal compression (solid plates versus belts).
    Voluntary breath hold.
    Assisted breath hold (air valve device).
    Respiratory gating.

Conventional Simulation

- The purpose of **SIM** is to do the following:
  - To set up a reproducible patient position and create any devices needed.
  - To select isocenters and beam angles that can be easily and reliably set up.
  - To take simulation films that can be used as a reference for treatment setup.
  - To obtain treatment planning data such as external contour and target volumes.
- The **SIM** should have the same isocentric setup as a treatment machine.
  - Light field, optical distance indicator (ODI).
- The isocenter filmed during **SIM** must be the same as the treatment isocenter.
- **Imaging**
  - Radiography ("plain film"): images are taken at PA, lateral, and each additional desired beam angle.
  - Fluoroscopy may be used for patient and isocenter positioning and for measuring breathing motion.
- **Patient data**
  - A conventional simulator is incapable of acquiring a detailed patient contour.
  - Wires, rods, calipers, and so on may be used to take measurements of the skin surface.
  - Target and avoidance volumes are defined on plain film.

CT Simulation

- Requires a **CT scan** encompassing all body parts that beams may enter or exit through.
- **CT** data can be directly used for computer-based dose calculations (**3D planning**).
- Isocenter skin marks are made at the time of **CT** but may be changed at the time of treatment ("iso shift").
- **Digitally reconstructed radiograph** (**DRR**)
  - A computer rendering that approximates a radiograph taken at an arbitrary angle and isocenter.
    Significantly worse resolution than a plain film.
    Resolution may be improved by using very thin slice CT.
  - Allows for selection of isocenter and beam angle after the time of simulation.

- **Volume rendering**
  - Contoured structures may be 3D rendered.
  - It is also possible to render density interfaces, such as blood vessels in lung or brain.
    This is commonly used in diagnostic radiology, not so much in radiation oncology.
- **Image registration**
  - Simulation CT may be registered ("fused") with outside imaging, such as prior CTs and MRs.
  - Various algorithms exist for rigid and deformable registration, treatment planning system (TPS) dependent.
- **Limitations of CT**
  - Patient pose must fit within the CT bore.
  - Field-of-view (**FOV**) is always smaller than the bore size.
    Artifacts occur if patient is too close to the bore.
  - Finite **slice thickness**.
    Craniocaudal resolution limited by slice thickness, unlike plain film which has sub-mm resolution in all directions.
  - **4D** technology is required to image breathing motion.

Verification Simulation

- Prior to the start of treatment, the isocenter position and each beam angle may be filmed to verify accurate setup.
- This may be done with:
  - Conventional simulator (2D)
  - kV and/or portal imaging on the linac (2D)
  - Verification CT on CT sim (3D)
  - Cone beam CT on the linac (3D)
  - Other devices (manufacturer dependent)

Portal Imaging

- **Portal imaging** visualizes the actual treatment field on the actual treatment machine.
  - **Single exposure**: only images the field itself.
  - **Double exposure**: exposed once with the treatment field and once with an open field, allowing a full field of view for normal anatomy.
- **Portal films**: there are two types of plain film:
  - **Localization film**: requires a few cGy to expose and may be used to image patient prior to treatment.
  - **Verification film**: requires ~2 Gy to expose and used to film the full-duration treatment.

– **Electronic portal imaging device** (**EPID**): faster than film, but size of image is limited by the size of the electronic imaging panel (generally smaller than a plain film).

3D Treatment Planning

- **3D planning requires:**
  - Use of CT data for target volume delineation.
  - Use of CT data for normal tissue delineation.
  - Use of CT data for radiation field design.
    Beam's eye views (BEVs) and DRRs.
- **3D beam angle selection**:
  - **Coplanar beams** do not include a couch kick. They will always be in the axial plane.
  - **Noncoplanar beams** use couch kicks and will enter and exit above or below the axial plane.
    Allow more freedom in selecting angles that avoid organs at risk.
    Drawbacks include: increased setup time and difficulty, collision risk, and requires extended CT scan length to encompass all beam entries.
- **3D structure sets** and d**ose-volume histograms**
  - A **DVH** is a method of displaying dose-volume statistics.
  - There are two basic types of **DVH** (Fig. 12.4).
  - DVHs allow you to visually judge how much dose a structure is receiving, and how homogeneous it is.
  - However, a DVH does not tell you **where** in a structure the high-dose and low-dose areas are located.
    Must review dose on actual images!

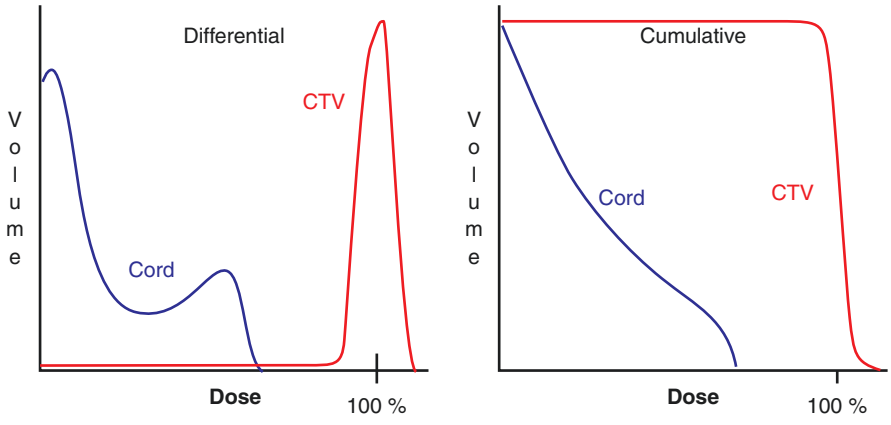

Fig. 12.4 Differential and cumulative DVHs. A differential DVH displays the volume of a structure receiving a dose. A cumulative DVH displays the volume of a structure receiving a dose or greater

- **Biological dose statistics**
  - **Tumor control probability** (**TCP**) is a synthetic number calculated by applying a chosen radiobiological formula to your DVH statistics.
  - **Normal tissue complication probability** (**NTCP**) is a similar value calculated for normal tissue toxicity.
  - **TCP** and **NTCP** concepts may be used for dose escalation or alternate fractionation calculations.

    These numbers are theoretical and not clinical (yet).

Non-IMRT Dose Optimization Techniques

- **Methods to increase CTV dose**:
  - Larger margins between CTV and block edge.

    At the cost of increased normal tissue dose.
  - Adding bolus.
- **Methods to improve normal tissue sparing**:
  - Smaller margins between CTV and block edge.

    At the cost of decreased CTV dose.
  - Choosing different beam angles to avoid specific organs.
  - Increased number of beam angles may increase **conformality** (decreased volume of high dose) at the cost of **integral dose** (increased volume of low dose).
- **Simple methods to improve dose homogeneity**:
  - Decrease beam weighting on the hot side.
  - Increase beam weighting on the cold side.
  - Add or adjust wedges, heels toward hot areas.
- **Complex methods to improve dose homogeneity**:
  - **Dose compensation**

    Use a physical or electronic compensator to selectively attenuate dose in areas that would otherwise be overdosed.
  - **Field within field** (aka "forward-planned IMRT")

    Treat the large field to a partial dose.

    Block the hot spots and treat the smaller field.

    If there are still hot spots, block those hot spots and continue treating an even smaller field.

Intensity-Modulated Radiotherapy (IMRT)

- **Inverse planned IMRT** uses inverse-planning software to calculate **nonhomogenous fluence maps**.
  - This contrasts with the "flatness" of an open field (Fig. 12.5).
- **IMRT optimization software**:
  - Physician provides dose constraints. A computer algorithm calculates a set of optimal **fluence maps** that attempt to meet the constraints.
  - Various algorithms exist including "simulated annealing" and "Pareto front optimization."

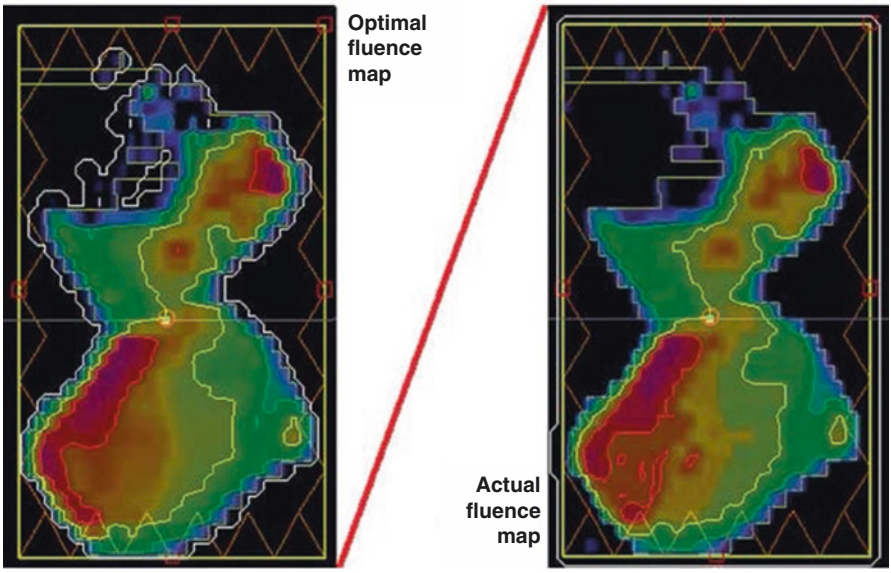

Fig. 12.5 IMRT fluence maps. Most treatment planning algorithms first compute "optimal fluence maps" (fluence desired by algorithm) and then convert these to "actual fluence maps" (fluence deliverable by linac). Some algorithms are capable of direct aperture optimization, optimizing linac and MLC movements without going through an intermediate step

- **IMRT delivery**:
  - **Fixed gantry techniques**
    Step-and-shoot: Each aperture is broken down into a number of segments. In between segments, the beam is turned off.
    Slid**ing window**: Each aperture is treated with continuously moving MLC leaves while the beam is on.
  - **Arc-based techniques** (**RapidArc**, **VMAT**, **etc**.)
    Continuous gantry movement with continuous MLC movement with the beam on.
    Requires specialized hardware and software.
  - **Helical tomotherapy**
    A specialized machine that delivers dose continuously while rotating around the patient in a CT-like fashion.
    Very good at conformality, but unable to utilize noncoplanar angles (close axial distance between CTV and OAR is difficult).
  - **Robotic**
    Beam delivery from many different beam angles ("nodes") chosen from a map of possible robot arm positions.
  - **Intensity-modulated proton therapy** (**IMPT**)
    Spot scanning with a proton pencil beam. Dose cloud is created by summation of many Bragg peaks.
    Please refer to Chap. 18 (Proton Beams) for more information.

Linac Quality Assurance

13

Introduction

Quality assurance is designed to ensure that radiation is delivered correctly. American association of physicist in medicine (AAPM) TG-40 and TG-142 recommendations set a standard of practice for radiation oncology practices. Machine characteristics are measured on a daily, monthly, and annual basis and compared to tolerance levels (unacceptable in the long term) and action levels (unacceptable at any time). Different devices are used to measure these quality assurance (QA) checks. Daily checks can use less precise but less cumbersome instruments, while monthly and annual checks use more precise instruments.

What Is Quality Assurance?

- **AAPM definition of QA**: "To assure that machine characteristics do not deviate significantly from their baseline values acquired at the time of testing and commissioning."
  - Linac measurements are taken during acceptance and commissioning.
  - The **AAPM** requires daily, monthly, and annual QA tests to ensure that linacs are able to deliver treatment as planned.
  - **TG-40** set standards for basic linacs without MLCs, on-board imaging, or respiratory gating.
  - **TG-142** newest guidlines that adds standards for multileaf collimators (MLCs), intensity modulated radiation therapy (IMRT), stereotactic body radiotherapy (SBRT), on-board imaging, and respiratory gating.
- **QA intervals and instrumentation**:
  - **Daily QA** may be done using relatively imprecise "spot check" instruments such as a daily QA device.

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  - **Monthly QA** should use more precise instrumentation than **daily QA**, as determined by the physicist based on national/international guidelines.
  - **Annual QA** should use the most precise commissioned instruments, including **TG-51** calibration with National Institute for Standards and Technology (**NIST**)-traceable ion chambers.
- **Tolerance level and action level**:
  - The **tolerance levels** are considered "acceptable" for clinical treatment.
    Tolerances are typically **3**% for daily checks, **2**% for monthly/annual checks, or **1**% for stereotactic.
    If the equipment consistently violates tolerance levels, treatment should be stopped until the equipment is brought into compliance.
  - However, **daily output checks** may be more variable due to their rapid and imprecise nature.
    An **action level** of **5**% is recommended for stopping treatment after a daily output check deviation.
    If the deviation is between **3**% and **5**%, treatment may continue "for the short term" until the discrepancy can be addressed.

Who Is Responsible for QA?

- The **chief radiation oncologist** (aka **physician director**) is ultimately responsible for everything that relates to patient care, including the proper functioning of equipment.
- A **qualified medical physicist** (**QMP**) should lead the **QA** team.
  - The **QMP** is responsible for knowing how to operate and interpret **QA** equipment and for training other personnel to use the **QA** equipment.
  - A **quality assurance committee** (**QAC**) should include at least one physician, physicist, and therapist.

Linac Regulations and Recommendations (TG-142)

- **Daily QA**
  - ±3% X-ray and electron output constancy
  - ±2 mm laser line accuracy (1 mm for SRS)
  - ±2 mm collimator size indicator (1 mm for SRS)
  - ±2 mm optical distance indicator (ODI) accuracy
  - **Functional**: door interlock, door closing safety, audiovisual monitors, radiation area monitor, beam on indicator, stereotactic lockouts (if applicable)
- **Monthly QA**
  - ±2% X-ray and electron output constancy
  - ±2% backup monitor chamber constancy
  - ±2% dose rate output constancy
  - ±1% X-ray and electron beam profile constancy (central axis percent depth dose, PDD/ tisssue maximu ratio, TMR)

  - ±2% electron energy constancy
  - ±2 mm/1% light field – radiation coincidence (1 mm/1% on each side)
  - ±1 mm laser distance check device
  - ±1° gantry/collimator angle indicators
  - ±2 mm accessory trays (i.e., graticules)
  - ±2 mm jaw position indicators (1 mm for asymmetric)
  - ±1 mm cross-hair centering
  - ±2 mm/1° couch position indicators (1 mm/0.5° for SRS)
  - ±2 mm wedge placement accuracy
  - ±1 mm compensator placement accuracy (for IMRT compensators)
  - ±2 mm localizing laser accuracy (1 mm for IMRT/SRS)
  - **Functional**: wedge and block latching, laser guard interlock, respiratory gating (if applicable)
- **Annual QA**
  - ±1% X-ray and electron flatness and symmetry change from baseline
  - ±1.0 MU/2% SRS arc MU set versus delivered
  - ±1.0/2% SRS arc rotation set versus delivered
  - ±1% X-ray and electron output calibration in a water phantom (TG-51)
  - ±1% X-ray field size output factor ($\geq 4 \times 4$ cm^2)
  - ±2% X-ray small-field size output factor ($<4 \times 4$ cm^2)
  - ±2% electron applicator output factor
  - ±1% X-ray beam quality (PDD10 or TMR10)
  - ±1 mm electron beam quality (R50)
  - ±2% physical wedge transmission factor constancy
  - ±2% X-ray and electron output constancy (≥5 MU)
  - ±5% X-ray output constancy (2–4 MU)
  - ±2% X-ray output constancy versus dose rate
  - ±1% X-ray and electron output constancy versus gantry angle
  - ±1% X-ray and electron off-axis factor versus gantry angle
  - ±1 mm collimator rotation isocenter
  - ±1 mm gantry rotation isocenter
  - ±1 mm couch rotation isocenter
  - **Functional** electron applicator interlocks
  - ±2 mm radiation–mechanical isocenter coincidence (1 mm for SRS)
  - ±2 mm tabletop sag
  - ±1° table angle
  - ±2 mm table maximum range of movement
  - **Functional** stereotactic accessories and interlocks

Additional Linac QA

- **TG-142** has additional daily, weekly, monthly, and annual QA guidelines for devices and treatment modes such as:
  - **Multileaf collimators**
  - **Nonphysical, soft wedges**

  - **Static and dynamic IMRT**
  - **On-board imaging devices (MV, kV, and CBCT)**
  - **Total body irradiation (TBI)**
  - **Total skin electron treatment (TSET)**
  - **Respiratory gating**
- These are too lengthy to list here.
- Note that all **weekly QA** applies to linac add-ons (MLCs, on-board imaging, etc.).
  - There is no **weekly QA** for basic linac functions.

Measurement Techniques

- **Daily QA** tasks are performed by the therapists, with rapid dosimetry equipment that can check many things at once.
  - For example, a square- or cube-shaped dose monitor (flat-panel detector or ion chamber array) can check linac **output**, **flatness** and **symmetry**, **laser alignment**, **field size**, and **ODI** all at the same time.
  - The **qualified medical physicist** (**QMP**) must be notified of any out-of-tolerance results.
- **Monthly QA** should be performed or directly supervised by the **QMP**.
  - Either the equipment should be **different from** the daily QA equipment or **cross-calibration** of the daily QA equipment should be performed.
- **Annual QA** must be performed by the **QMP** and must use water phantoms and calibrated NIST-traceable ion chambers.

Radiation Protection and Safety

14

Introduction

Radiation protection is a necessary process to reduce dose to radiation workers and the general public. There are multiple bodies that regulate various aspects of radiation protection including the International Commission on Radiological Protection (ICRP), National Council on Radiation Protection and Measurements (NCRP), Nuclear Regulatory Commission (NRC), state governments, the food and drug adminstration (FDA), and the US department of transportation. Adverse radiation effects can be divided into either stochastic or non-stochastic effects and the dose limits to individuals and bodily organs predicated on historical epidemiological and animal measurements of these effects. When designing shielding for linear accelerators, many factors come into play, depending on the type of radiation, the workload, use, and occupancy on the other side of the shield. In addition to radiation shielding, there are multiple procedures and administrative requirements to ensure safe delivery of radiation.

Regulatory Bodies (USA)

- Protection standards, including annual dose limits, are set by the **ICRP** internationally and the **NCRP** nationally.
- **NRC** – these are the guys who license all **nuclear reactor produced** materials or byproduct material.
- **Individual State Agencies/Laws** – oversee naturally occurring radioactive material, cyclotron produced material (generally positron emitting stuff), and all types of X-ray generators.
- **DOT** (department of transportation) oversees **transport** of radioactive material.
- **FDA** oversees pharmaceutical aspects of radioactive material.

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Types of Radiation Effects and Limits

- **Stochastic and non-stochastic effects** (please see Chap. 34):
  - Non-stochastic or deterministic effects are effects that occur after a certain threshold dose.
  - Stochastic (random) effects are probabilistic with no lower safe threshold.
- **Measurements**:
  - For radiation protection, we use **Sieverts (Sv) or millisieverts (mSv)** instead of Gray or any other measurements of dose or exposure (see Chap. 6).
- Dose limits for Areas:
  - **Unrestricted areas: 0.02 mSv/h (or 2 mrem/h)** or 0.1 mSv/week (10 mrem/week) for shielding calculations.
- Dose limits for general public per year, intermittent exposure:
  - **Total – 5 mSv** (including embryo or fetus undeclared).
  - **Lens of eye – 15 mSv**
  - **Other organs – 50 mSv**
- Dose limits for radiation workers:
  - **Multiply general public limits by 10**
  - Total – 50 mSv total body
  - Lens of eye – 50 mGy (see Chap. 35)
  - Other organs – 500 mSv
  - (There are no fetal radiation workers.)
- Children or general public in continuous exposure situations **should not get > 1 mSv**.
- Fetus declared is **0.5 mSv/month** (which is almost the same as five total for undeclared).
- Appropriate visitors to hospitalized brachytherapy patients may get up to **5 mSv** (Figs. 14.1 and 14.2).

Structural Shielding Design for External Beam Therapy: How to Build a Bunker

- **This is basic guildlines for how to build a bunker, however, we strongly recommend that a professional shielding expert be hired to do this job. TERMS: know these terms**!!! (from NCRP reports 49, 51, 149, and 151).
  - **Primary barriers –** the walls behind the main target areas, must be able to protect against the direct beam.
  - **W (workload) –** total weekly radiation delivered. Expressed in milliampere minutes per week (maximal mA × minutes of beam-on time) for equipment below 500 kvp (diagnostic).

    For megavoltage machines, expressed as weekly dose delivered at 1 m from the source (**cGy/week at 1 m**) – this can be estimated by multiplying number of patients per week by the dose per fraction (since SAD calculations have dose to isocenter which is usually at 1 m). Assuming 250 patients per week (50 per day) with 200 cGy per fraction (standard fractionation), that comes to a workload of around 50,000 cGy/week.

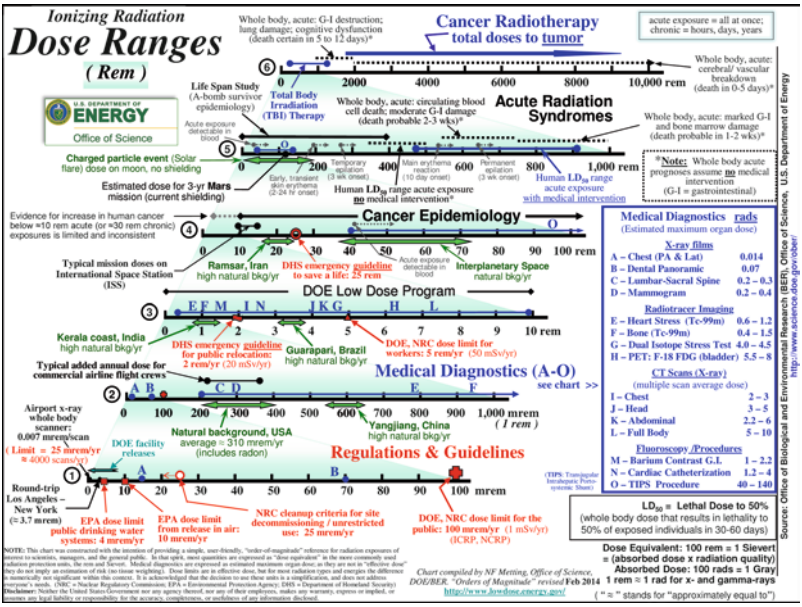

Fig. 14.1 Ionizing radiation dose ranges measured in Rem (older measurement of equivalent dose). (Source: Office of Biological and Environmental Research (BER), Office of Science, US Department of Energy, http://www.science.doe.gov/ober/)

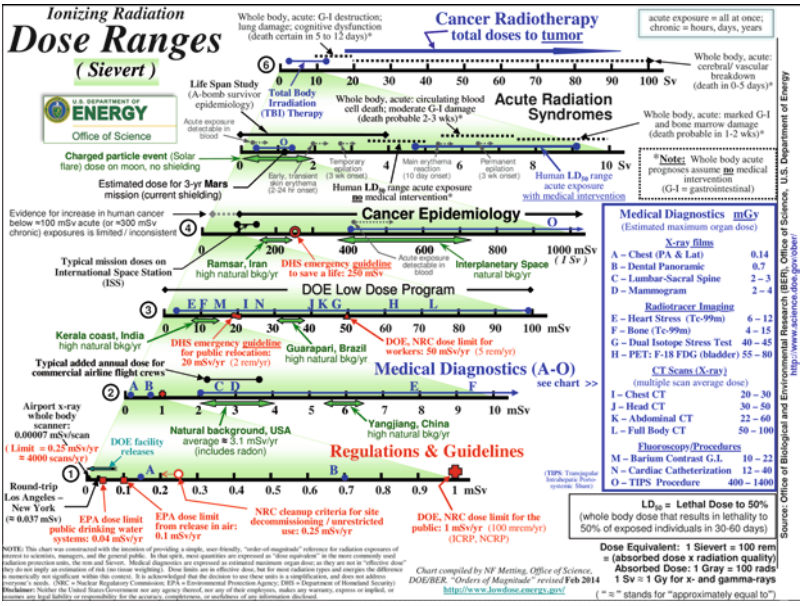

Fig. 14.2 Ionizing radiation dose ranges measured in Sieverts (SI units). (Source: Office of Biological and Environmental Research (BER), Office of Science, U.S. Department of Energy, http://www.science.doe.gov/ober/)

- **U (use factor)** – fraction of operating time during which the radiation is directed toward a particular barrier or wall.
  If you do a lot of 10-field intensity modulated radiation therapy (IMRT), it will be all over the place. If you do all opposed laterals, it will be split 50% on the right and left walls.
  If you do all total body irradiation (TBI), or total skin irradiation (TSI), it will be 100% on one wall.
  Use factor in secondary barrier calculations is always 100% or 1 for all barriers, as secondary scatter is present regardless of where the beam is aimed.
  Floor should usually be 1 (for all the single field things you do).
  Ceiling should be ¼–½ depending on techniques.
  Walls are usually ¼.
- **T (occupancy factor) –** fraction of operating time during which the area is occupied. Someone actually tabulated the following relative occupancy times:
  Full occupancy (T = 1) – work areas, offices, nurses' stations.
  Partial occupancy (T = 1/4) – corridors, restrooms.
  Occasional occupancy (T = 1/8 1/16) – waiting rooms, stairways, elevators, outside areas, janitor closets.
  Zero occupancy (T = 0) – underground.
- **d (distance)** – distance in meters from radiation source (remember inverse square law – it is pretty important).
- **P** (permissible dose equivalent for area).
  Controlled area (overseen by radiation safety officer) – **0.1 cGy/week**.
  Uncontrolled area – **0.01 cGy/week**.

$$P = \frac{\mathrm{WUT}}{d^2} \times B \tag{14.1}$$

- **B** – transmission factor of a barrier to reduce the expected radiation to P level. This is dependent on energy.
  Before you start pouring concrete for your brand new fancy machine, use this equation to figure out how thick it needs to be for each wall or door:

$$B = \frac{P \times d^2}{\mathrm{WUT}} \tag{14.2}$$

- Concrete is what is typically used for Linac vaults.
- There are tables for the amount of various materials needed for various transmission factors (B) usually described in tenth-value layers or TVL's that can be found in NCRP report 51 or NCRP report 144.
- As a rule of thumb, **8.6 ft or 260 cm of concrete** is usually sufficient as a primary barrier for a machine running up to 18 MV photons.

Secondary Barriers

- Meant to protect against **Scatter** and **Leakage**, not the direct beam.
- This mostly applies to the walls of off-axis areas that will not have the beam pointed at it.

- Secondary shielding is usually half of the primary barrier (where there is no primary barrier).
  - So if you do not want to think, **just use 130 cm or 4.3 ft of concrete that will be adequate!**
- Use factor **(U) is always 1** and hence is no longer in the equations.
- More terms for secondary barrier equations:
  - **α – ratio of scattered to incident exposure**.
    Varies for different angles and for different beam energies.
    There are tables in NCRP report 51 and 151 but just remember 0.1% or 0**.001** which is α at 90° from the primary beam.
  - **F** – area of the beam incident at the scatterer.
    Usually this is multiplied by 1/400 because 400 cm^2 is the area of the beam for which α is given.
    (If your area happens to be around 400 cm^2, the term drops out.)
  - **d′** – distance from the scatterer to the area of interest (again used in inverse square fashion).
  - $\mathbf{B_s}$ – Barrier transmission for scatter factors.
  - $\mathbf{B_L}$ – Barrier transmission for leakage factors.
- **Scatter equations**:

$$B_s = \frac{P \times d^2}{\mathrm{WUT}} \times \frac{400 d'^2}{\alpha F} \tag{14.3}$$

- Now assuming U = 1 and α = 0.001, Eq. 14.3 can be rewritten as follows:

$$B_s = \frac{P \times d^2 d'^2}{0.001 \times \mathrm{WT}} \times \frac{400}{F} \tag{14.4}$$

  (where 400/F will be close to 1 or so).
- **Leakage**
  - NCRP report 102 states regulations for leakage limits, but regardless, you will always have some leakage and should **use 0.1% (multiply workload by 0.001) for the leakage factor**.

$$B_S = \frac{P \times d^2}{0.001 \times \mathrm{WT}} \tag{14.5}$$

- **Machine shielding** (beam stoppers and head shielding) – some linacs have beam stoppers built within the machine to come out behind the patient when using high energy modes (16 MV) to help people with shielding if their vaults were only made to 6 MV or cobalt specifications. Head shielding is also present to prevent leakage and scatter. Head leakage is not allowed to be more than 0.1% of the useful beam.
- **Doors** – doors to linac rooms need to have the same shielding factors as walls and typically are gigantic and made of lots of high atomic number (Z) metal (usually lead) with neutron shielding (borated polyethylene – see next). In order to help with this, use a Maze.
- Maze – if you want a smaller door that can open significantly faster, a good configuration is a maze. This allows for far less shielding in the door because most

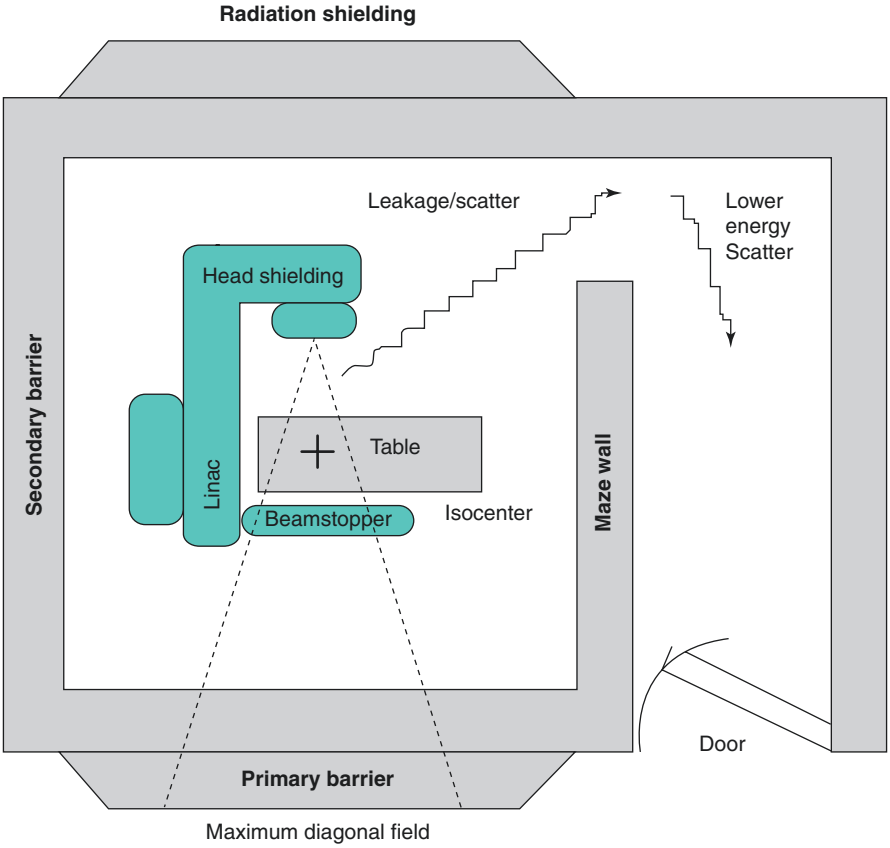

Fig. 14.3 A typical radiation shielding around a linear accelerator

of the radiation at the door will be from radiation that has already scattered many times and can be estimated at 500 kVp, meaning you only need about 6 mm of lead (about a quarter of an inch) (Fig. 14.3).

Neutron Shielding

- Photonuclear Disintegration.
  - When linacs operate at energies >10 MV, you can sometimes get photonuclear disintegrations in the walls or targets of the linac – this produces neutrons at a broad spectrum but maxing out at about 1 MeV (see Chap. 4).
  - Since neutrons are relatively heavy and uncharged, they interact far more with nuclei (especially hydrogen) than with electrons, so electron density does not matter as much as having lots of nuclei around.
  - **Wax** or **borated polyethylene** (boron and carbon atoms connected to **LOTS of hydrogen atoms**) work great to slow down fast neutrons (thermalize them)

so that they can be stopped. As neutron is captured, it produces capture gammas that are stopped with the lead or steel shielding on a door.
- Concrete works great too, so the shielding you use for X-rays will usually work fine for walls – furthermore, maze configurations are also excellent for protecting the door, especially if they are >5 m.
- When neutrons slow down or stop, they can release X-rays (inelastic scatter, see Chap. 5) or gamma rays from neutron capture reactions in the shielding.
  This means that if you do not expect the neutrons to slow down significantly from a good maze, you will need a lot of lead on the door to protect against those secondary photons.
  These photons can be as high as 8 MeV but are usually around 1 MeV.

Radiation Protection for Brachytherapy Procedures

- Whenever dealing with safety for radioactive sources, it is important to always remember three factors: **Time** (as little time exposed as possible), **Distance** (radiation falls off from a point source by the inverse square law), and **Shielding** (keep big heavy barriers between yourself and the source).
- **Source storage and transport containers** – sources should be sealed in lead-lined safes with lead-lined drawers and the areas should be ventilated directly to the outside.
  - An L-Block should be available to load and unload the sources within the "hot-room."
  - Lead-lined safe carts ("pigs") should be used to cart around the radioactive material to its intended destination.
- **Patient room** – shielding for brachytherapy follows the same rules as external beam shielding with workload, used factor, occupancy, and the same permissible requirements.
  - In General, a high dose rate (HDR) room must be specifically licensed as such (not just any shielded room). With that said, old linac vaults will usually pass the tests.
  - The tenth-value layer thickness (TVL – amount of material required to reduce an incident beam to 1/10 of its initial intensity) for Cobalt-60 and Cesium-137 are 39.8 mm and 21.6 mm for lead and 19.9 and 16.6 cm for concrete respectively. This is much lower than what is required for even a 6 MV linear accelerator: 56.1 mm lead or 34.5 cm concrete.
- **Special considerations for HDR brachytherapy** – make sure to perform the required source shielding tests for the afterloader after any maintenance (including source changes). Also make sure that personnel know how to respond in an emergency (how to make the source retract).
- **Release of patients treated with temporary implants.**
  - Patients who have received either implantable brachytherapy or unsealed sources may be "released into the wild" if it is unlikely that any innocent bystanders would ever receive more than 5 mSv or 0.5 rem (remember the public limits from earlier?).

Table 14.1 Activities and dose rates at 1 m from the patient before they may be released into the general public

Radionuclide	Activity (mCi)	Dose rate @ 1 m (mSv/h)
I-125	9	0.01
Pd-103	40	0.03
Ir-192	2	0.008
I-131	33	0.07

  - You must provide written instructions to the patient (or caretakers, parents, etc.) regarding keeping dose as low as possible if the dose is expected to be greater than 1 mSv or 0.1 rem.
  - Additional requirements include the following measurements from NRC regulatory guide 8.39: (Table 14.1).
- **Leak testing of sealed sources** – sealed sources must be tested for leaks about every 6 months and records must be kept for 3 years. If there exists 185 Bq (0.005 mCi) of removable contamination, you must take the source and either fix it, store it, or dispose of it and then file a report to the NRC in 5 days.
- **Routine radiation surveys** – surveys must be performed after a source is implanted and after it is removed. Surveys must also be performed routinely around source safes (storage safes and afterloader safes) to ensure that radiation levels do not exceed the Sealed Source and Device Registry. Surveys should be repeated after any repairs, installations, or source replacements.
- **Personnel monitoring** – basically, everyone working in a controlled area must use personal dosimeters (TLD badge, TLD ring, film badge, electronic dosimeter, OSL, etc.). Official definitions for who should wear one are anyone expected to receive 25% of the maximum permissible dose (NCRP definition) or 10% of the maximum permissible dose (NRC definition).
- **Protection against nonionizing radiation** – make sure to wear sunscreen outside and do not look directly at the treatment room lasers.

Administrative Requirements

- In order to be a licensee of radioactive material by the NRC, there are **three main requirements** to be submitted:
  - **Request for license application**, renewal or amendment before submitting to the NRC.
  - **Authorized users (AU),** (usually a radiation oncologist who logs lots of time in brachytherapy or GK or an interventional radiologist who uses a lot of unsealed source injections), or an authorized nuclear pharmacist (ANP), or an authorized medical physicist (AMP).
  - **Radiation protection program** changes that do require a license amendment.
- In general, a licensee must also report Medical events to the NRC and the patient within 24 h, with a written report in 15 days.

  - The precise definition of a medical event changes frequently with NRC bureaucracy (and you should stay up to date as to what those are), but in general, medical events almost always include the following:
    Delivered doses that are different from what was intended
    Treating the wrong target
    Wrong patient
    Any serious medical consequences or deaths that were an accident
- There are a few positions that are mandated by the NRC as well:
  - **Radiation Safety Officer (RSO)** – responsible for implementing the radiation protection program – authority, duties, and responsibilities must be submitted in writing.
  - **Radiation Safety Committee** – if a licensee uses more than one type of radioactive material, there must be a safety committee that oversees all of it. It must include the following:
    RSO – by default
    An **authorized user** (usually the prescribing physician)
    A representative of the **nursing** service
    A representative of **management** who is not the RSO or an authorized user
  - **Radiopharmaceutical Therapy** – the authorized user must possess a dose calibrator that can measure the activity administered to each patient. Otherwise, follow the safety precautions and regulations previously described for brachytherapy.

Final Notes

- This chapter has attempted to outline the broad concepts and important specifics for radiation safety; however, it is not meant to be used as a reference. For official guidelines, one should consult the NRC and NCRP guidelines as well as any state laws that may apply.
  - http://www.nrc.gov/
  - http://www.ncrponline.org/

Quality Management Program

15

Introduction

The Nuclear Regulatory Commission (NRC) is responsible for regulating nuclear material, including any nuclides used in brachytherapy. All medical sources are classified as nuclear byproduct material. The use of byproduct material requires an authorized user (physician), AU and an authorised medical physicist (AMP) or radiation safety officer, as well as a written directive and a quality management program (QMP). Deviations from the written directive may be classified as medical events (misadministration) depending on their severity.

Radionuclide Regulations and the NRC

- The Nuclear Regulatory Commission (**NRC**) has the power to regulate **nuclear material** in the USA.
- **Nuclear material** comes in three categories:
  - **Nuclear source material**: Naturally occurring uranium and thorium.
  - **Special nuclear material**: Enriched uranium (^{235}**U**) and plutonium (^{239}**Pu**). This material is "special" because it can be used in nuclear weapons.
  - **Nuclear byproduct material**: All artificially produced radioactive nuclides other than plutonium, plus naturally occurring ^{226}**Ra**, and tailings or waste from uranium and thorium mining and processing.
- For radiotherapy purposes, we are only concerned with **nuclear byproduct material**.
- The **NRC** does not regulate:
  - X-ray, electron, proton, or ion therapy.
  - Naturally occurring radionuclides other than uranium, thorium, or radium.
- The **NRC** has delegated its authority to several **agreement states**, allowing those states to regulate **byproduct material** within their own borders.

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  - In **non-agreement states**, the **NRC** directly regulates byproduct material.
- The concept of **written directives** and **medical events** (**misadministration**) was originated by the **NRC**, but each state has its own regulations for X-ray and electron therapy.
- All use of byproduct material must be supervised by an **authorized user** or **authorized nuclear pharmacist** identified on an NRC license.
  - **Authorized users** are usually nuclear medicine or radiation oncology MDs.
- A **Radiation Safety Officer (RSO)** must be appointed with the responsibility to:
  - **Identify radiation safety problems.**
  - **Initiate, recommend, or provide corrective actions.**
  - **Stop unsafe operations.**
  - **Verify** implementation of corrective actions.
- **Written directives** must be documented and followed for all "therapeutic dose" radionuclide use.
- Initial nuclide **activity** is measured by an NRC licensed manufacturer, preparer, or producer, and should be measured by the licensee prior to patient use.
  - **Activity** should be mathematically corrected for decay if it decays by $\geq 1\%$.
- A **source inventory** of all byproduct materials, except for gamma knife sources, must be performed every **6 months**:
  - Source **type**, **number**, physical **location**, and **activity** must be recorded.
  - **Leak testing** should be performed for all **sealed sources** with a half-life exceeding 30 days, except for ^{192}**Ir** ribbons.
  - Records must be kept for at least 3 years.

Quality Management Program/Plan (QMP)

- A **QMP** is a set of written procedures that ensures that radiation is administered as ordered.
- The exact regulations for a **QMP** vary between the NRC and various states, but are generally similar.
- The basic idea behind a **QMP** is the following:
  - A licensed **practitioner** (AU) must sign a **written directive** that includes patient, site, radiation modality, and dose.
  - There must be a **quality assurance mechanism** to ensure that dose calculations are done properly, that the **written directive** is followed, and that any deviations from the written directive are documented.
    For linac radiotherapy, this generally includes some form of **weekly chart check**.
  - The identity of non-practitioner operators (radiation therapists) must be documented.
  - There must be a mechanism for written **revisions** to **written directives**.
  - There must be a mechanism to document and report accidental events (**misadministration** or **medical events**).
- Each radiotherapy institution must have its own **QMP** that is approved by the state (for linacs) and by the **NRC RSO** (for brachy).

Written Directive (NRC)

- A **written directive** is required for ^{131}**I** doses exceeding 30 μCi, and for any "therapeutic" dosage of radiation from a byproduct material.
- In the case of medical emergency, an oral directive is acceptable but a **written directive** must be signed within 48 h.
- The **written directive** must contain the patient's name and the following:
  - **Unsealed sources**: Radioactive drug, dose, and route of administration.
  - **Gamma knife**: Dose, treatment sites, and target coordinates for each treatment site.
  - **Teletherapy**: Total dose, dose per fraction, number of fractions, and treatment site.
  - **High Dose rate (HDR) brachytherapy**: Nuclide, treatment site, total dose, dose per fraction, and number of fractions.
  - **Non-HDR brachytherapy**:
    Before implantation: Treatment site, nuclide, and dose.
    After implantation but before completion of the procedure: Nuclide, treatment site, number of sources, and total source strength and exposure time (or total dose).
- A written **revision** to a **written directive** must be dated and signed prior to the revised treatment.
- Copies of written directives must be kept for a minimum of **3 years**.

Medical Event, aka Misadministration

- The **NRC** changed the name from **misadministration** to **medical events**.
  - Many state regulations still use the word **misadministration**, so a linac accident may still be called a **misadministration**.
- **Medical events** include all of the following:
  - **Wrong dose** (±20% of total dose or ± 50% of a single fraction).
  - **Wrong drug** (different nuclide or chemical composition).
  - **Wrong patient.**
  - **Wrong site**, excluding migration of correctly implanted permanent seeds.
  - **Wrong mode** of treatment (such as low dose rate (LDR) instead of HDR).
  - **A leaking sealed source.**
  - Any event that results in or will result in unintended permanent functional damage as determined by a physician.
- The incorrect dose exceeds 0.05 Sv to the total body or 0.5 Sv to the skin, a single organ, or tissue.
- All **medical events** must be reported within 24 h to:
  - The referring physician.
  - The subject of the medical event, or an appropriate responsible relative or guardian, unless telling the individual would be harmful or the individual cannot be reached.
  - The NRC Operations Center.
- State regulations for linac accidents are generally very similar to NRC regulations for radionuclide accidents.

Special Topics: Computers

16

Introduction

With the advent of computers and especially with 3D conformal radiotherapy, the use of Patient Archiving and Communication System and common Digital Imaging and Communications in Medicine files has become increasingly important. Also of importance is the understanding of the various three-dimensional treatment planning systems including measurement-based systems, Monte Carlo, pencil beam, convolution/superposition, and collapsed cone algorithms. It is also important to understand the concept of simulated annealing for the purpose of intensity-modulated radiotherapy planning.

Computers: Miscellaneous Topics that Are Important!

- **DICOM** – **D**igital **I**maging and **C**ommunications in **M**edicine – is the standard format for medical imaging. Version 3.0 was developed in 1993 but for some reason, there are still some departments that do not use this. If you ever request films from an outside facility, it would be wise to request that they are in either DICOM or DICOM-RT format.
  - DICOM files also batch important information about the file such as patient name, ID, date of birth, slice thickness, kVp, and pixel representation.
  - DICOM-RT files can include contouring structures, dose, and radiotherapy plans.
  - Pixel representation is how the data are sent – either big bytes first (big Endian) or little bytes first (little Endian).
  - There are many variations of the DICOM features. Many freeware programs on the internet are available that can read non-standard imaging files. Usually, imaging studies when loaded on a compact disk also carry the read in format data that may be slightly different than DICOM-RT format.

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- PACS – Patient Archiving and Communication System

  PACS provides massive data storage from any imaging device on a single platform. Every hospital usually has its own PACS system and just about all of them will accept DICOM files (though unfortunately, not all will generate them naturally, but they can usually convert their own file format into DICOM). Huge amount of storage and further reading of any study is made possible by a PACS.

Image Registration

- In the treatment of cancer with radiation, often we use CT scans, MRIs, or PET scans that are taken on completely different days and are often reconstructed in three dimensions using different algorithms for many reasons:
  - Resolving and understanding the change in target due to growth or reduction or weight gain or loss.
  - Defining structure sets from uniqueness of imaging modalities such as CT, MRI, and PET.
- **Image registration** is a process to unify various images into a single coordinate system for visualizing multiple image sets taken at different points in time, different modalities, and different conditions of the same patient.
  - Positron emission tomography

    Image registration in PET imaging had been a difficult process due to the loss of anatomical information. Thanks to the innovation of the CT-PET device, registration is seamless as data are taken in a single coordinate system where anatomy is displayed on the physiological image in the same coordinate.

    There continues to be a slight problem in CT-PET due to temporal variation as images are taken at different time phase (you still cannot run them both at the EXACT same time); however, such problems have not been a major issue and active research is continuing to improve temporal changes in PET images by gated PET imaging.
  - CT-CT/CT-MRI

    Many algorithms are available.
    - Point to point mapping.
    - Surface matching.
    - Pixel by pixel matching.
    - Interactive, and mutual information.
- Algorithms in general can be divided into linear (rigid) and elastic (non-rigid) transformation.
  - The **linear transformation** (rigid) uses rotation, scaling, and translation to match images.
  - The **elastic matching** uses additional features of elastically distorting a pixel based on tissue characterization and is an example of **deformable registration.**

Example: The ability to fuse images of the neck in the flexed and extended positions or fusing images of a child in different phases of growth.
There are several types of software in the market that provide satisfactory deformable registration such as Velocity and MIM.

- **Image fusion**
  - When images are set in a single coordinate system, any two images can be registered within that single coordinate system and hence called image fusion.
  - Fused images could be created from single or multi-modality images such as CT, MRI, and PET.
  - The image fusion mechanism provides viewing of two images superimposed on each other. One can select the weight (transparency) of image to view one or other image set.
  - This provides opportunity to draw contours of MRI to CT or from PET to CT data set for treatment planning.
    Example: In radiosurgery application, CT, MRI, and angiographic images are also fused to view the details of abnormalities.
    Example: In prostate cancer, ultrasound images are fused to CT data set for brachytherapy treatment.

Treatment Planning Software

- **Measurement-based (based off empirical historical data.**
  - May be used on 2D or 3D data sets.
  - Based on measured data in water phantoms.
    Accounts for correction factors for surface irregularities, beam modifiers, and tissue heterogeneity.
  - Relatively reliable for regular fields and fewer required corrections and less reliable for more complex treatments like IMRT.
  - Examples:
    Hand-calculations (SAD/SSD-based)
    TAR/TMR
    Batho
    Power law
    Clarkson method
    MRI-based stereotactic brain treatments (based on measurements since there is no electron density data set).
- **Model-based (all modern CT-based treatment systems)**
  - Rely on 3D CT data sets – cannot be used on 2D data sets.
  - Usually based on simplified equations derived from Monte Carlo simulations (see below).
  - Generally accurate for homogenous and non-homogenous (bone, lung, metallic interfaces), and irregular fields with non-uniform fluence.
  - Monte **Carlo** – best of model-based calculations for all radiation types.

Calculates potential "**histories**" or theoretical particle path lengths using the physical constants of both the particles and the medium along with probabilistic equations and other complex physics equations for **each particle that enters the body** (billions of calculations) (Fig. 16.1).

All events and byproducts of interactions are accounted for as they travel in media.

This is the standard by which all other model-based calculations are measured.

Requires very large computing capabilities and not practical for regular use with present-day technology as of this writing (perhaps in the future though).

There are multiple different Monte Carlo programs compiled for different settings and different particles. Examples:

- EGS (Electron Gamma Shower)
- Penelope
- FLUKA
- GEANT
- MCNP

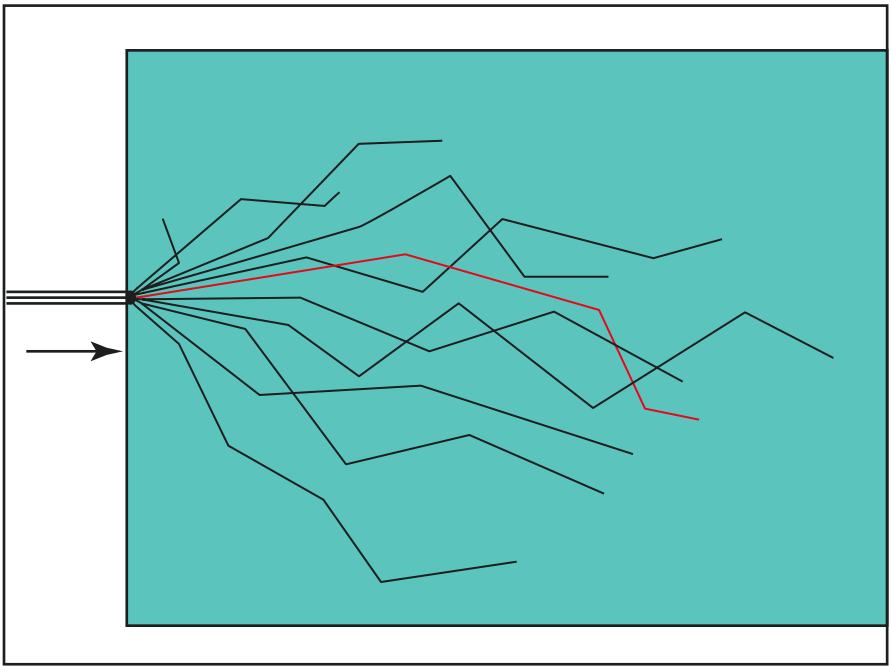

Fig. 16.1 Monte Carlo algorithm: Each potential particle history is mapped using physical constants and interaction probabilities. As the number of histories increases, the accuracy of the model increases. Mapping 2 Gy of radiation over a 3 cm × 3 cm field would require close to 10^{11} histories, which is not reasonable for present-day machines; however, 10^{7} histories come extremely close to an exact distribution and are achievable

– **Pencil beam**.
  Photon interacts with medium and produces electrons.
  Electrons tend to have tortuous paths with multiple angle changes as they bounce around from coulombic forces. A pencil beam algorithm assumes that these scattering angles are small and therefore a beam about the size of a pencil should scatter out in a Gaussian distribution (bell curve) at all depths.
  Wide-angle scattering actually happens in reality (and can be modeled through Monte Carlo simulations), but this is expected to be minimal in homogenous material and is therefore left out of the equations.
  The isodose plot of a pencil beam calculated from these equations looks like a tear-drop for electrons, and when spread over a large field, this closely resembles observations of actual homogenous dose distributions.
  This algorithm is most accurate in the central region of large regular fields. It is still reasonably accurate at contour irregularities and in the penumbra region.
  The algorithm tends to fail with inhomogeneities (crossing from tissue into bone or air). This is especially true where the inhomogeneity is smaller than the pencil beam spread or instances of multiple inhomogeneities (Fig. 16.2).
– **Convolution/superposition**
  Utilizes both Monte Carlo–derived parameters and analytically derived calculations.
  Convolution is a mathematical operation using two functions to produce a third function that is typically viewed as a modified version of one of the initial two.

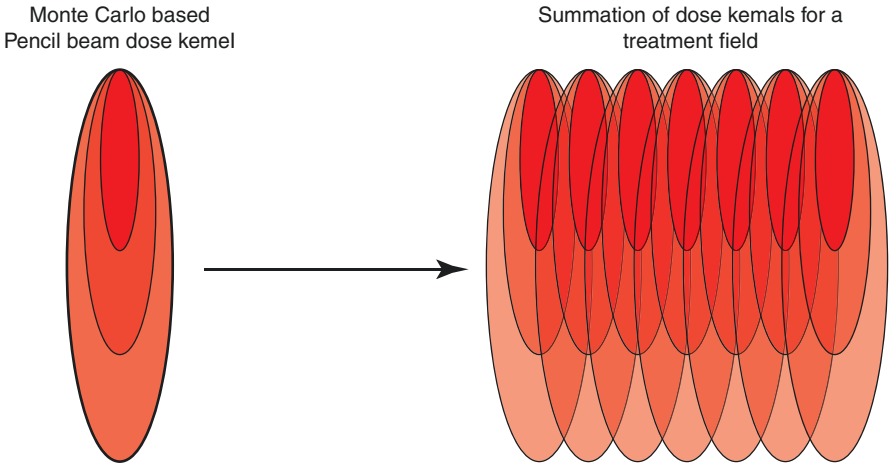

Fig. 16.2 Pencil beam algorithm for calculating dose: A pencil beam distribution is approximated using Monte Carlo methods and then these pencil beams are stacked to approximate a treatment field. Colors represent isodose levels

Consists of two separate functions that are integrated:

- **TERMA** – **T**otal **E**nergy **R**eleased in **M**edia by photons (related to collision KERMA).
- **Kernel** – **primary dose** and **scatter** dose from photons, expressed separately either as a pencil beam (see above) or as a point (more accurate).

Heavy weight is placed on the primary photons and less weight on scattered photons. Subsequently, a separate kernel accounts for electrons set in motion away from the primary photon – this is based on Monte Carlo simulations.

Early convolution models (without superposition) used only Monte Carlo–based pencil beam approximations of primary dose but excluded any scatter dose.

- Works well in flat homogenous fields.
- Breaks down in heterogeneity (similar to pencil beam).

Superposition adds the scatter factors – both photons and electrons.

There are separate functions for the tungsten target, flattening filter, collimators, and other modifiers that operate on the dose kernel equation.

Attenuation of the beam is accounted for by CT number of each voxel within the CT simulation scan.

– **Collapsed Cone Convolution Superposition**

Radiation dose is deposited by the secondary particles that carry the energy extracted (from the beam) some distance away where they are created.

This process goes into all directions (360°) from all irradiated locations. A fast calculation method to estimate this is to divide the directions of energy spread into discrete cones that each is collapsed into a line, and arranging such lines all over the space where the dose is to be calculated.

The energy flow along such a line collects and redistributes the dose deposition spread in the directions of the cone where the line stems from.

The shape is governed by beam energy and medium where interaction is taking place.

In short, collapsed cone is a fast and extremely accurate dose calculation method that estimates the energy transport and dose deposition caused by secondary particles in photon beams by dividing the full sphere of scatter directions into a set of discrete cones that are collapsed and represented by their central axis directions.

These collapsed cones then can be used with usually convolution/superposition concept as described above.

Most treatment planning software vendors utilize this method under proprietary names (example: Eclipse – AAA algorithm by Varian).

– Further advancements in treatment algorithms rely on solving the Boltzmann transport equation and can closely approximate Monte Carlo simulations (example: Acuros by Varian).

Simulated Annealing (Inverse Planning in IMRT)

- For intensity-modulated radiotherapy (IMRT), one strategy is to manually plan a treatment to give the most conformal dose with the greatest sparing of normal tissues – alternatively one could instead plug in a set of variables and have a computer come up with an answer.
- Simulated annealing is a mathematical system using cost functions and probabilistic search procedures to provide global minimizations of the function.
  - Factors that go into the program:
    Target volumes and organ at risk (OAR) volumes.
    Prescription dose.
    Dose tolerances (max, min, dose-volume histogram parameters, etc.).
    Level of importance (is it more important to spare normal tissues or cover the target with maximal dose).
    Gradient "tightness" – how much of a dose gradient are you willing to accept between a target and an organ at risk.
    - Gradients that are too loose will result in bad plans.
    - Gradients that are too tight will usually fail IMRT QA (quality assurance) and will also raise the importance of treatment setup to avoid target underdose and OAR overdose.

    OPTIONAL – beam angles and beam sizes.
  - How it works (in general):
    The computer will come up with a rough plan based on the initial parameters (arbitrary initial state).
    The computer will then make a tweak to the weight or fluence map of one or more beams and compare with the previous state to see if it is a better plan or if it is a worse plan.
    This tweaking step is repeated thousands of times, each time moving to a lower minimum state.
    - Initially, large tweaks.
    - Gradually, smaller tweaks as it appears that the algorithm is reaching a local minimum state (achieving the best mix of cost functions by their hierarchical order).
    - Sometimes, optimizations can become stuck in a non-optimum state such that small tweaks in any direction do not appear to produce a better plan but it is not the absolute minimal state (not the optimal plan).
    - The local minimum is saved and then the algorithm either restarts or starts making large tweaks again to see if it could find a better local minimum (Fig. 16.3).

    The total number of solutions to a treatment plan (good or bad) is nearly infinite. The longer you let the simulated annealing plan work, the better plan you will get.
    - Theoretically, if you let the program run infinitely, you could find a perfect plan.

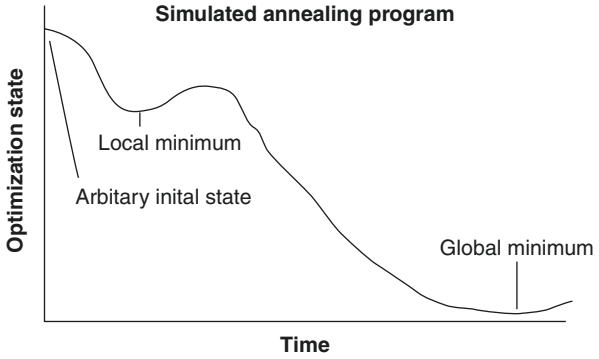

Fig. 16.3 Simulated annealing program: The program starts with an initial treatment plan (arbitrary initial state) – it then tweaks the plan many times, searching for a better plan iteratively. Eventually, the program reaches a solution where small tweaks do not improve the plan (local minimum) so it makes a large jump and continues tweaking until it reaches the global minimum (the best overall plan)

MRI-Linear Accelerator (MRL)

17

Introduction

MRI-Linac is a new device that combines an MRI unit and a 6 MV linear accelerator (on a single circular gantry) very similar to a tomotherapy unit for image-guided and adaptive therapy. It uses MRI for planning and image guidance. This device is most useful for treating soft tissue tumors such as liver, pancreas, kidney, and so on. The MRI signal is converted to a pseudo-CT called synthetic CT for planning and dose calculation. Using a fast MLC on a linac, this device provides on-line image verification and intensity modulated radiation therapy (IMRT), volumentric modulated arc therapy (VMAT) treatment.

Nuclear Magnetic Resonance

- Larmor constant (γ) or gyromagnetic ratio (MHz/Tesla).
  - Precession frequency is directly proportional to the external magnetic field.
  - This is unique to each nucleus.
- Magnetic resonance imaging (MRI).
  - Gradients in the magnetic field are directly related to the differences in resonance.
  - Gradients in the magnetic field can be exploited to create two-dimensional images.
- Protons have spin momentum and act like a magnetic dipole or microscopic compass needle.
  - Human body consists mainly of water with an abundance of hydrogen nuclei (protons).
  - Different tissues in the body have different water or hydrogen contents.
  - When the body is exposed to a strong magnetic field, hydrogen nuclei align with it.

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When a pulse of radio waves is introduced from an orthogonal direction, energy content of the nuclei changes.

After the RF pulse, a resonance wave is emitted as the nuclei try to return to the previous state (relax).

Small differences in the oscillations of the nuclei can be detected as they relax.

By using computer processing, the magnetic gradients can be combined into a 3D image reflecting the differences in hydrogen contents in the tissues.

- Relaxation times.

  T1 (relaxation time 1) relates to the time it takes nuclei to relax or reach the original condition aligned to the external magnetic field after the radio frequency is turned off.

  T2 (relaxation time 2) is the relaxation time to dephase (loss of phase coherence among precessing nuclei) in the transverse plane.

  T1 and T2 have distinct tissue characteristics and images acquired are described as being T1-weighted or T2-weighted.

- Nuclear magnetic resonance imaging (nMRI or just MRI) is the imaging of choice for soft tissue structures and is able to show subtle tissue differentiation in tumors (Fig. 17.1).
  - MR images are suited to radiotherapy for soft tissue organs such as liver, kidney, pancreas, brain, and so on.
  - Ideally, MR should be used for treatment planning; however, treatment planning requires electron density information which is not achieved on MR imaging.
  - Historically, MRI data have been fused with CT data for planning.

    Prone to errors in positional accuracy while image fusion.

    Prone to errors due to reference setup, table structure, and lack of immobilization.

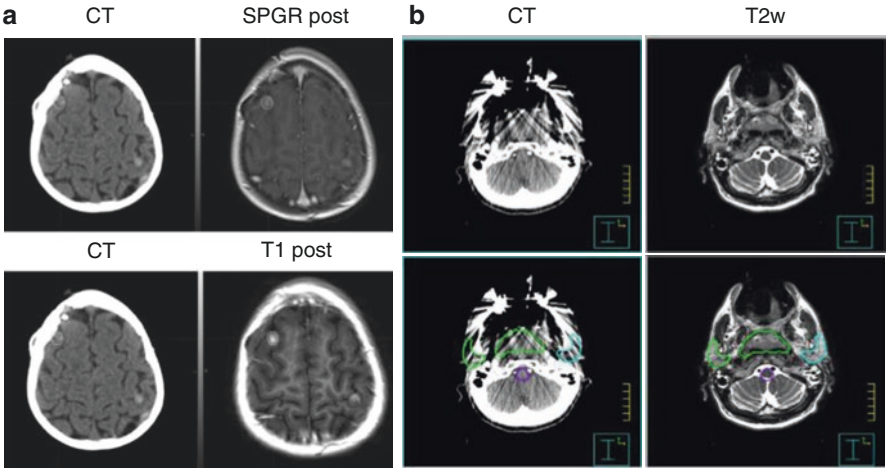

Fig. 17.1 (**a**) A small brain lesion is invisible in CT images, but can be clearly distinguished in MR images, (**b**) another patient with a dental filling for which CT images are difficult to provide volume delineation. (Adapted with permission from Das et al., Br J Radiol 2018; 91: 20180505)

MR Simulation

- Historically limited success due to low magnetic field (poor image quality) and lack of process for converting MR images for dose calculation.
- Prosthetic devices that produce CT artifact can often be overcome with MRI (Fig. 17.1b).
- CT-MR fusion or device integration is often required (MRI + CBCT).

MRI Integration with Adaptive Therapy

- Integration is a technical challenge since radio-frequency, magnetic field, and accelerator operation with its own RF frequency cannot be easily integrated.
- Historical prototypes included.
  - MRI/accelerator in a long room on rails.
  - MRI with 3 Co-60 sources with MLC.
- Co-60 source is not ideal due to radiation safety, terrorism, dose rate, and source decay issues.
- Several models are now commercially available with integrated MRI and linear accelerator (Fig. 17.2).

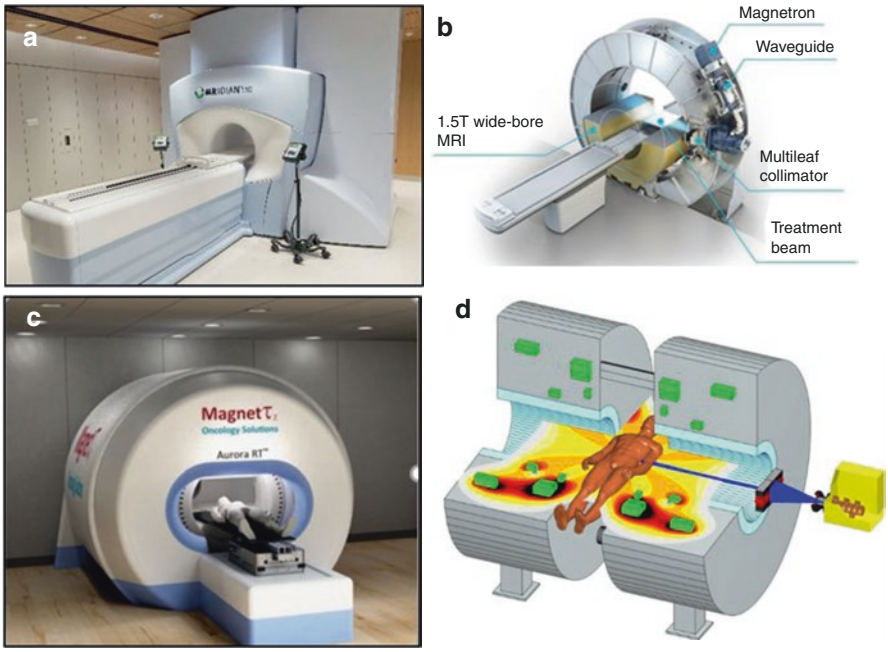

Fig. 17.2 (**a**) ViewRay MRIdian system, (**b**) Elekta Unity1.5 T MRI-Linac, (**c**) Alberta's Aurora RT system, and (**d**) Australian (Sydney) MRI System in preparation. (Adapted with permission from Das et al., Br J Radiol 2018; 91: 20180505)

Problems in MRI-Based Treatment

- Patient selection.
  - Metallic implants.
  - Cardiac pacemaker/defibrillators.
  - Patient size and immobilization devices related to bore size.
  - Patients with clastrophobia.
- Magnetic field.
  - Some risks to magnetic field with certain patients.
  - Care should be taken to maintain uniformity of magnetic field or else image distortions can occur.
- Safety issues.
  - Magnetic fields carry some danger by themselves (see Table 17.1).
  - Apart from Table 17.1, the combined effect of radiation and magnetic field should be evaluated and proper precautions adopted, especially for skin erythema which could be related to many issues related to the radiation buildup or the magnetic effects.

- Geometric distortion.
  - Unique to MRI as an imaging modality
  - Uneven scaling of voxel away from the center is noted and has large implications in terms of image perception and volumetric analysis as shown in Fig. 17.3.
  - Can be due to imperfections in magnetic field, differences in tissue composition, and chemical shift (Fig. 17.3).
  - Geometric distortion is dependent on pulse sequences, mainly gradient recalled echo (GRE) and spin echo.

    GRE produces more pronounced distortions than spin echo and chemical shift.

Table 17.1 MRI adverse event incidences in the USA compiled by US Food and Drug Administration (FDA)

MRI adverse event category	Number (%)
Thermal (blister, burns, heating fire, etc.)	906 (59)
Mechanical (slips, falls, crush injuries, broken bones, and cuts)	170 (11)
Projectile (objects pulled into magnetic field)	133 (9)
Miscellaneous (sufficient narrative)	109 (7)
Image quality (lost, misoriented, inadequate, or mislabeled images)	89 (6)
Acoustic (hearing loss and/or tinnitus)	86 (6)
Unclear (connection to the MRI exam is unclear)	55 (4)
Death (12 cases)[a]	0 (0)
Total	1548 (100)

[a]FDA removed the 12 death cases and placed them into a separate category for investigations

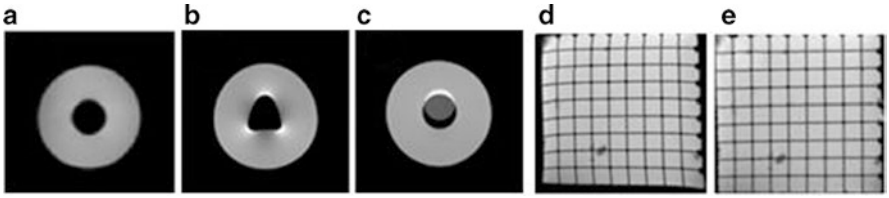

Fig. 17.3 Distortions in MRI images are shown: (**a**) original image, (**b**) geometric distortion, and (**c**) chemical shift distortion. Using phantom geometric distortion is eliminated as shown: (**d**) original image and (**e**) corrected image. (Adapted from Crijns et al., PMB, 56, 289, 2012)

- Geometric distortion is a complex process that depends on magnetic field imperfection, pulse sequence, imaging parameters, and patient anatomy.
- Typical distortions are <2 mm away from isocenter. Distortion is minimal or zero in the center of the field (Fig. 17.3).
- Manufacturers have various methods to quantify distortion but mainly grid phantom is imaged and a correction factor is applied to each voxel based on distortion.
- Geometric distortion should be measured periodically in the QA process.
- MRI distortions are more typically and significant for higher field strength, despite the better image quality.

Electron Return Effect (ERE)

- Magnetic fields cause dosimetric issues due to the **Lorentz effect**.
- Any charged particle in a magnetic field, B, experiences a force (F = BeV) and makes the particle move in a circle with a centripetal force ($F = mv^2/r$) where:
  - m is mass
  - v is velocity of the charged particle
  - r is the radius of the circle
- One can easily imagine scenarios where electrons ejected in a medium from a photon interaction (photoelectric, Compton scatter, pair production) experience a magnetic field effect and cause a dose pattern that would not have occurred without the magnetic field.
- Effect is more severe with increasing magnetic field.
- Effect can be pronounced with tissue interface situations (air, lung, and breast).
- If the effect is properly characterized, this effect can be accounted for in the treatment planning system.
- Treatment planner should be aware not to ignore any hot spots at air tissue interfaces (see Fig. 17.4).
- Aurora system attempts to get around this by using a lower strength magnetic field (0.5 T) in a perpendicular direction and the beam entry being through a hole.

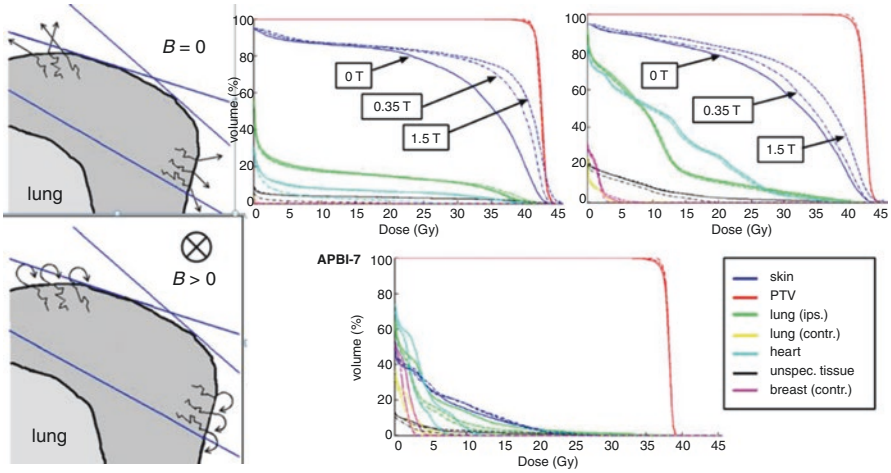

Fig. 17.4 Effect of magnetic field on breast treatment. Please note that electrons return to the skin surface in the magnetic field, thus increasing the dose. Also note the DVH with increasing field. (Adapted with permission from Van Heijst et al., Phys Med Biol 585,917–5930, 2013)

Dosimetric Problem: Calibration

- Typical dosimetry calibration with ion chambers use national/international protocols and assume that secondary electrons created by photon interactions (photoelectric effect, Compton scatter, pair production) move freely without a magnetic field.
- Lorentz fields cause secondary electrons to change their paths.
  - This violates the Bragg–Gray cavity theory.
  - Dosimetry is therefore more uncertain.
  - This aspect can be simulated using Monte Carlo.
- Most detectors, including film (EBT), produce dose perturbations that need to be considered properly.
- Figure 17.5 shows the implications of the magnetic field.
  - At air–water tissue interfaces, electron transport can be serious enough to produce dose perturbation and discontinuities that may have implications for patient care.

Training Issues

- Many physicists are not trained in MRI or MRI-Linac (MRL) crossover.
- For MRL QA, a physicist should have a good understanding of the MRI and linear accelerator.
- Therapists similarly should have proper training in operation and safety.
- Strong cross-disciplinary collaboration between therapy and diagnostic physicists and technologists is essential.

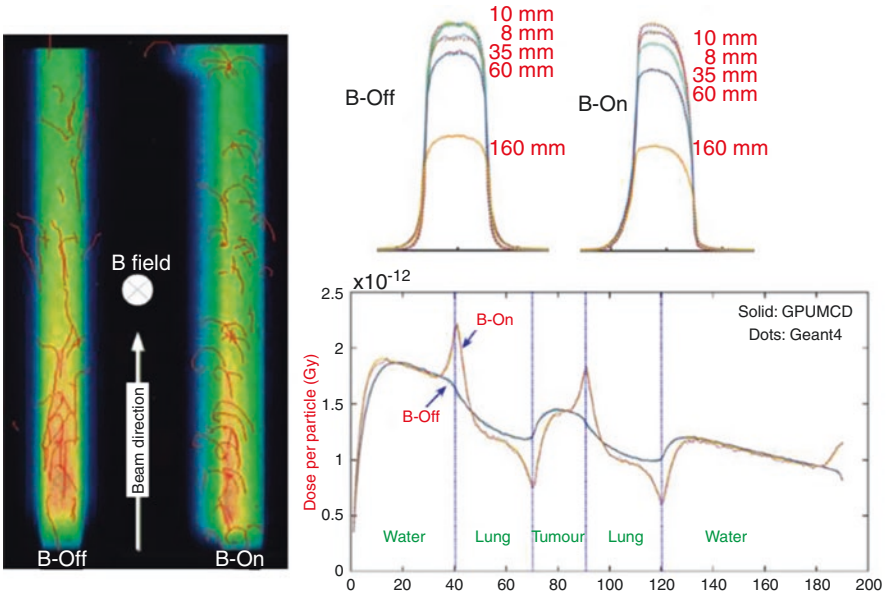

Fig. 17.5 Effect of magnetic fields on electron track. In the left panel electron tracks are shown bending outward in magnetic fields. This causes problem in profiles and depth dose in homogeneous and heterogeneous medium as shown in the upper and lower panel. Note the electrons bend in magnetic field thus producing distortion in profiles and depth dose with discontinuity at the interfaces. In water/air or air/water the electron transport in magnetic field is so serious that it produces significant dose perturbation and discontinuities that may have implications for patient care. (Adapted with permission from Ahmad et al. Med Phys 43(2), 894–907, 2016)

- Diagnostic physicists can play a vital role in the implementation of an MRL in a radiation oncology department.
- The FDA provides emphasis that everyone in patient care should be aware of the unique safety challenges associated with MR environments, thus reducing preventable adverse event rate to a minimum.

Synthetic CT

- Dose calculations are performed based on electron density, typically derived from CT data.
- CT number represents an attenuation coefficient map of tissue (Fig. 17.6).
- Electron density can correlate for each scanner, providing a link between CT ➔electron density ➔ dose.
- MRI signal is a complex function of magnetic field, gradient field, acquisition technique, and relaxation times of tissues and therefore is not easily directly linked to electron density (Fig. 17.6).
- To use MRI signal for treatment planning, MR signal in each voxel should be converted to CT number (synthetic CT or sCT) to be used for dose calculation.

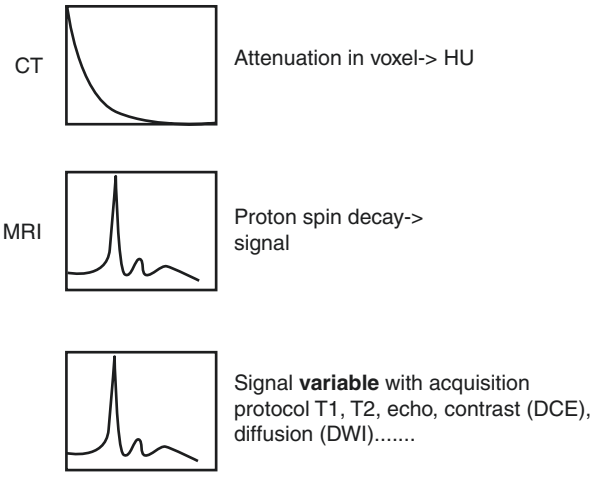

Fig. 17.6 Illustrating the signal in a voxel in CT and MRI. Please note that in MRI, it is very subjective and a characteristic value of the tissue cannot be assigned

Dixon Method

- Atlas-based method that maps electron densities to MRI scans.
- Uses data for four tissues (air, fat, lung, soft tissue).
- Correlated linearly to create sCT in tissues.
- Works nicely if bone is ignored.
- Can work nicely for prostate cancer (see Fig. 17.7).
- Dosimetric accuracy can be very high where volume is soft tissue like (dose difference of ± 1.5%).
- Larger differences are noted when there are interfaces (air/tissue, bone/tissue).

Interpolation (ICRU Table)

- A workaround process as ICRU has tabulated attenuation coefficient of tissues for a given energy and physical electron density.
- For a given tissue, MR signal can be linked to an attenuation coefficient (CT).
- Not as popular since it is a tabular process.

Machine Learning, AI, CNN

- Artificial intelligence (AI) or convoluted neural network (CNN) can be used for creating sCT more accurately for all tissues compared to Dixon method, which works well for soft tissue.
- Large amounts of patient data with known MRI signal and corresponding CT data are used to train the system to create a map of MRI to CT.
- Training data set must be very large.
- Figure 17.8 demonstrates brain case using CNN to create sCT.

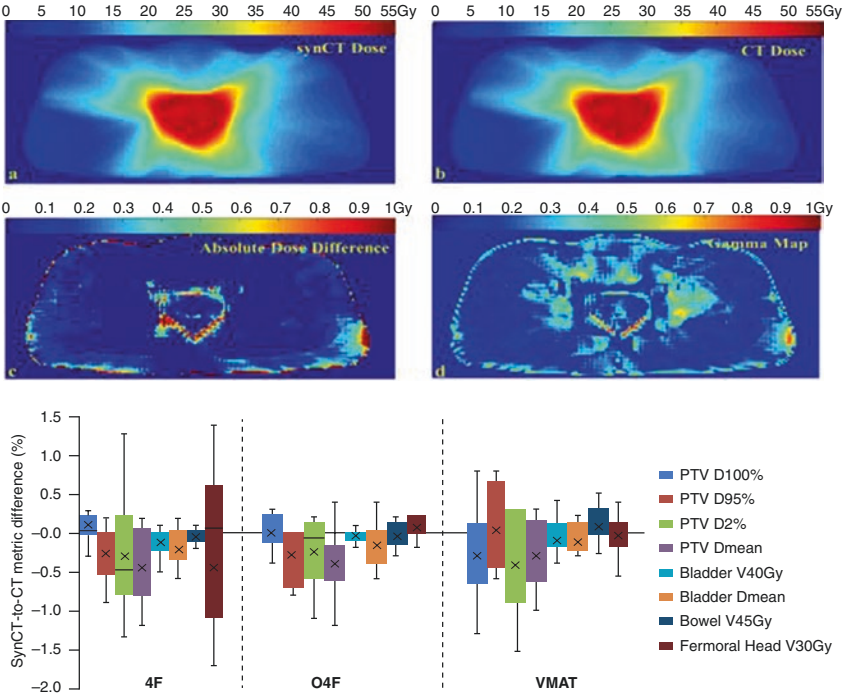

Fig. 17.7 (Upper panel) dose distribution of a prostate patient using sCT and CT. The corresponding dose difference and gamma maps are also shown. The lower panel shows the numerical values between treatment plan on sCT and CT. Please note that the dose differences in the four field (4F), 4F oblique and VMAT plans are minimal within ±1.5%. (Adapted from Wang et al., PLoS ONE 13(1): e0190883, 2018)

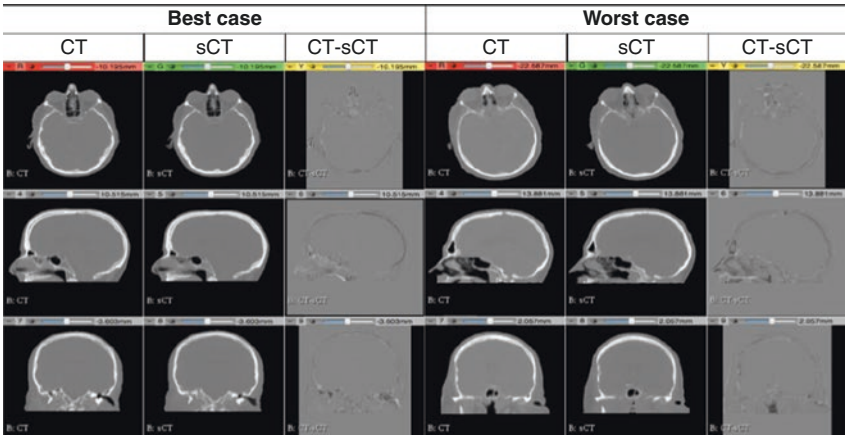

Fig. 17.8 CNN-based sCT of head and neck patients; best case (left) and worst case (right). Note that CNN provides very accurate presentation of bone and soft tissue which other methods fail. Note that difference image (CT-sCT) in both cases are invisible indicative of very good quality sCT. (Adapted from Spadea et al., Int J Radiat Oncol Biol Phys, 105(3), 495–503, 2019)

Digitally Reconstructed Radiograph (DRR)

- A good DRR is required to reflect the physician's intended treatment volume in the beam's-eye-view.
- DRR is a byproduct of the CT simulation or treatment planning process.
- For MRL, sCT needs to be evaluated for treatment.
- Quality should be sufficiently good so that no error is introduced.
- For MRL, the process is typically integrated into the system and adaptive planning is one of the goals of MRL.
- Multiple algorithms exist to incorporate MRI data into an sCT and subsequently generate a DRR for treatment verification.

Motion Management

- MRI images can be used for motion management and adaptive therapy.
- MRI scans are obtained daily to reflect motion.
- Many researchers have proposed cine-MRI approach to acquire quick images and correct them appropriately.
- Since MRL units have robust MLC systems, they can provide adaptive therapy in relatively short time.
- Throughput of this system must be improved and time will tell if these units can be used as regular linear accelerators.

Protons

18

Introduction

Proton beams offer a therapeutic advantage of having a steep dose falloff at the end of their path. While a proton is moving fast, it typically has a small sphere of influence as a charged particle and has a relative biological effectiveness (RBE) similar to, but slightly higher than photons. As a proton slows, the linear energy transfer greatly increases until it reaches the Bragg peak, when it releases a great amount of energy and then subsequently the energy falls off rapidly to zero. In order to be clinically useful, the Bragg peak must be spread out. This is accomplished with a modulator wheel. Protons are typically generated from a cyclotron, a synchrocyclotron, or a synchrotron. The beam created from these devices can be further modulated to fit the clinical need. A more detailed particle interaction with medium is provided in the Chap. 5 of this book.

- **Proton Interaction**
  - **Energy loss governed by Bethe-Bloch equation (with minor modifications)**

$$\frac{dE}{\rho dx} = \frac{4\pi N_A r_e^2 m_e c^2}{\beta^2}\frac{Z}{A}z^2\left[\ln\left(\frac{2m_e c^2\beta^2}{I\left(1-\beta^2\right)}\right)-\beta^2\right] \tag{18.1}$$

E is the particle energy (MeV).
dE/dx is energy loss per unit distance x (MeV/cm).
ρ is the density of the medium.
N_A is Avogadro's number (6.022×10^{23}).
ρ_e is the classical electron radius (2.8179×10^{-15}m).
m_e is mass of electron ($9.10938356 \times 10^{-31}$ kg).
c is the velocity of light (299,792 km/s).

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z is charge of particle.
Z is atomic number of the medium.
A is the atomic mass of the medium.
β is relative velocity (v/c) of the particle.
I is the ionization potential of the medium.
Based on this equation, energy loss, which can be represented by linear energy transfer (LET) is proportional to z^2 and inversely proportional to the mass of the particle.

- Therefore, heavy particles have higher LET and higher RBE than protons.

- Stopping power is related to the speed of a particle and its relative sphere of influence (see Fig. 18.1).
  - Fast moving particles have less time to interact with the medium and have less energy loss.
  - Slow moving particles have more time and therefore a greater sphere of influence and also a higher energy loss.
  - As a particle slows down, the energy loss increases until it hits the Bragg peak (see Fig 18.2a). This was described by Robert Wilson in 1946 who proposed the use of fast proton for clinical use.
  - Range is inversely proportional to the stopping power and can be expressed with the following equation illustrating the relationship between proton energy and range:

$$R = \int_0^E \frac{dE}{(dE/dx).} \tag{18.2}$$

$$R\,(\text{cm}) = 0.033\,E + 0.0005E^2 \tag{18.3}$$

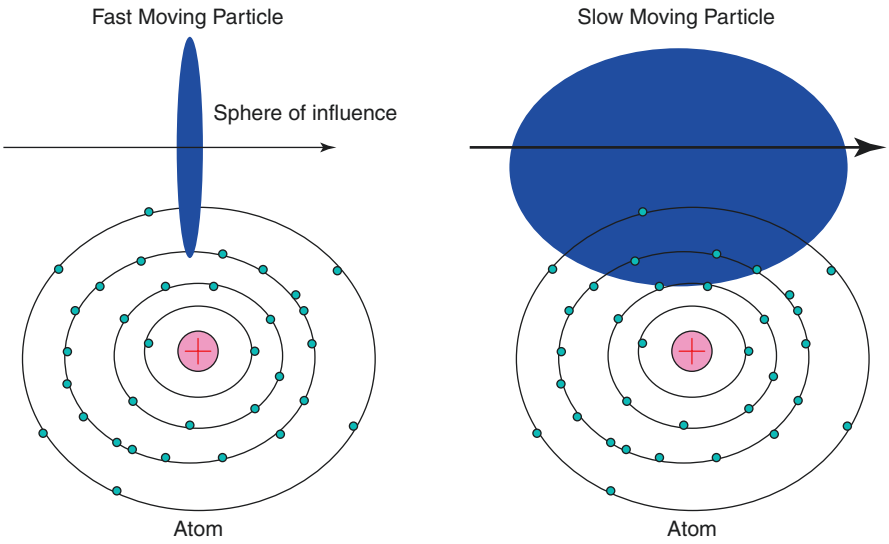

Fig. 18.1 Schematic of fast and slow moving particles influencing the atoms of the medium and thus losing energy based on their speed. Slow moving particle loses higher energy than fast moving

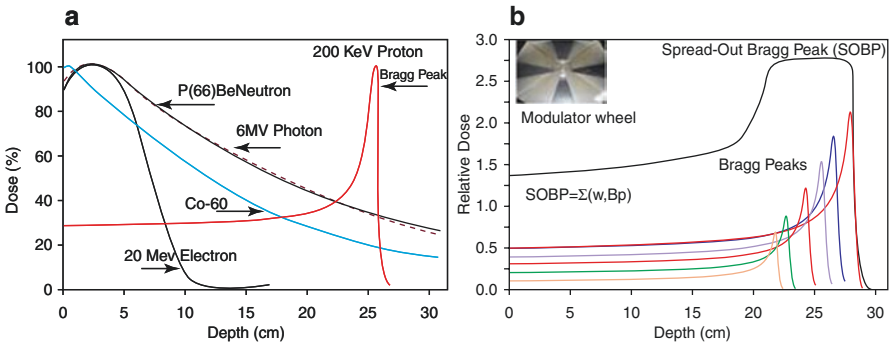

Fig. 18.2 (**a**) Comparison of the depth dose of various types of radiation. The proton beam has unique depth dose reflected with sharp dose rise known as Bragg peak. (**b**) The pristine Bragg peak can be broadened by modulator wheel (inset). Variable thickness of the wheel makes various types of Bragg peak reflected in the figure. A weighted sum of these peaks makes SOBP which is wide enough to cover the tumor

- Range straggling: Energy loss is statistical process due to the fact that particle interaction is probabilistic, and therefore actual range is somewhat random and fuzzy.
- Stopping power is one form of LET and can be expressed in the following equation:

$$\left(\frac{S}{\rho}\right)_{\text{air}}^{w} = 1.137 - 4.3\times10^{-5} R_{\text{res}} + \frac{1.84\times10^{-3}}{R_{\text{res}}} \tag{18.4}$$

  R_{res} = residual range
  S = stopping power
- Radiation dose in a medium is then directly related to stopping power as follows:
  Dose = ϕ • S/ρ
  (ϕ) = fluence or number of protons/cm^2
  Effectively, Number of protons/cm^2 • Mev/g cm^2 = MeV/g = > J/kg = Gy
  Therefore, in order to produce 1 Gy of dose, one needs billions of protons!

- **Proton Depth Dose**
  - As alluded to previously, the proton depth dose distribution begins with a low surface dose and rises as the particles lose velocity until they create the Bragg peak and drops rapidly (Figs. 18.2a and 18.3a).
  - Bragg peak is typically 2–3 mm wide and not suitable for any large size tumor.
  - Various strategies are used to make several small Bragg peaks and effectively spread out the Bragg peak to make it useful clinically.
    This can be achieved with a modulator wheel as seen in Fig. 18.3b.
    Modulator wheels can be interchanged and typically have a fixed length of SOBP.
  - Even a single proton beam with a carefully planned SOBP can be used to create uniform tumor coverage (see Figs. 18.3 for a single beam and 18.4 for parallel opposed beam).

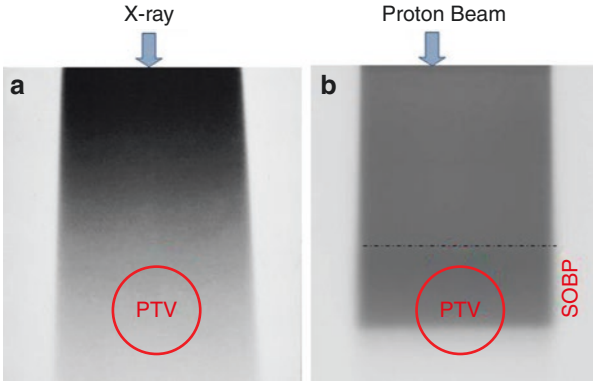

Fig. 18.3 Dose distribution in 2D plane is shown on a radiographic film (**a**) photon beam and (**b**) proton beam. Note uniform dose in PTV with proton beam

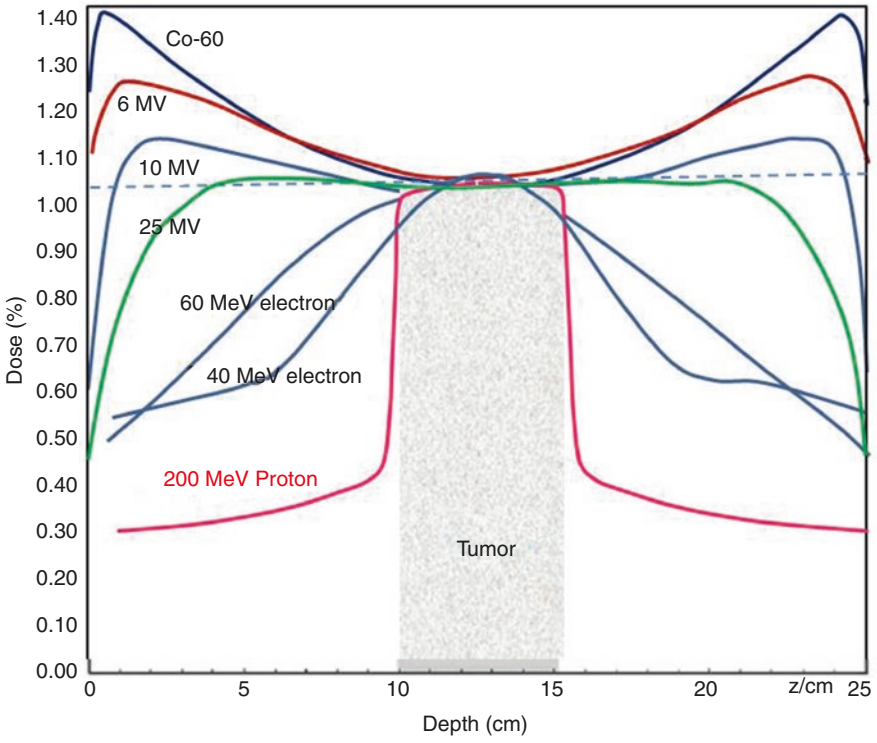

Fig. 18.4 Dose distribution of various radiation beams with parallel opposed beams. Note that the proton beam provides uniform dose to tumor with minimum dose to entrance and exit side

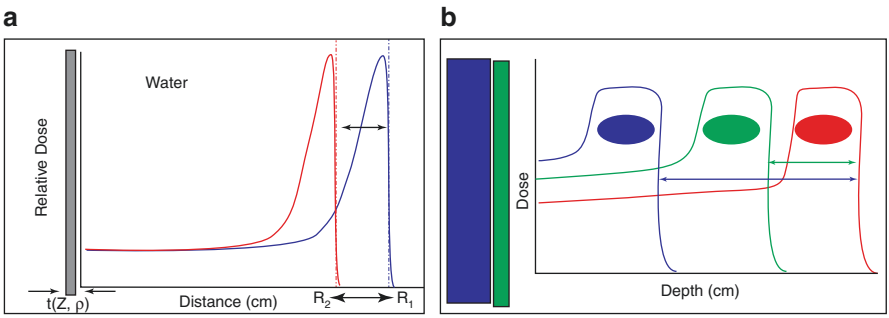

Fig. 18.5 (**a**) shows the range shift with material thickness in the front of surface. This is called WET, water equivalent thickness; (**b**) shows clinical cases where tumor is placed in SOBP but with different range or different depth in tissue. Note the cuve shifts with different amount of material placed in the front

  - Using SOBPs, more uniform tumor coverage can be achieved with protons than with other various radiation beams and also often with a lower number of beams (see Fig. 18.5).
- **Range Shift and Target Coverage**
  - Beam energy from a cyclotron/synchrotron is fixed (e.g., 250 MeV).
  - A low atomic number medium can be used to reduce the energy.
    Can be placed in the nozzle or the beamline.
    Thickness of the materials can be calculated based on stopping powers.
    Material thickness is known as water equivalent thickness (WET).
    Increasing WET pulls the Bragg peak closer to the surface (Fig. 18.5a).
    WET in the beamline is used for major energy shifts while WET in the nozzle (graphite plates) can be interchanged quickly.
- **Dose Distribution**
  - **Treatment planning systems can be used to optimize the dose distribution to cover a target and spare distal structures**.
    Example: craniospinal irradiation (Fig. 18.6).
  - **At shallow depths, proton beams provide a sharper penumbra (2–3 mm) than a photon beam (6–8 mm), and therefore protons also spare lateral tissue more effectively**.
  - **Due to the finite distal edge in a proton beam, this often means that proton beams will have superior dose distributions to IMRT (much lower integral dose and low dose spillage)**.
    See Fig. 18.7
- **Production of Proton Beams**
  - Cyclotron
    Two "D"s placed side by side in a strong magnetic field (see Fig. 18.8).
    Small gap where protons are injected.
    "D"s are connected to high power radio frequency (RF) that changes polarity of the "D"s.
    Protons travel in a circular path attracted to the negative pole as it alternates.

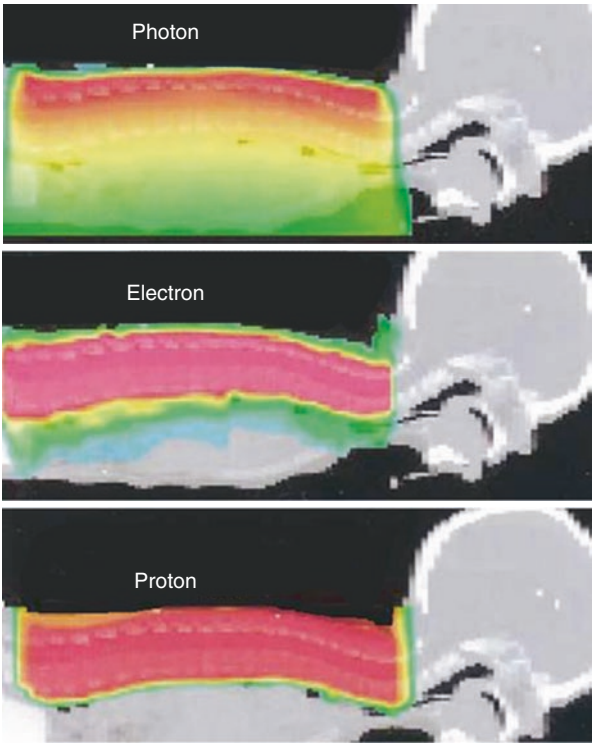

Fig. 18.6 Dose distribution comparison in a pediatric treatment of spinal axis in meduloblastoma. Top panel is for 6 MV photon beam, msiddle panel with 20 MeV electron beam, and lower panel with 200 MeV proton beam. Note significant sparing of normal tissue with the proton beam. (Reproduced with permission St Clair et al., Int J Radiat Oncol Biol Phys, 58, 3, 727–734, 2004)

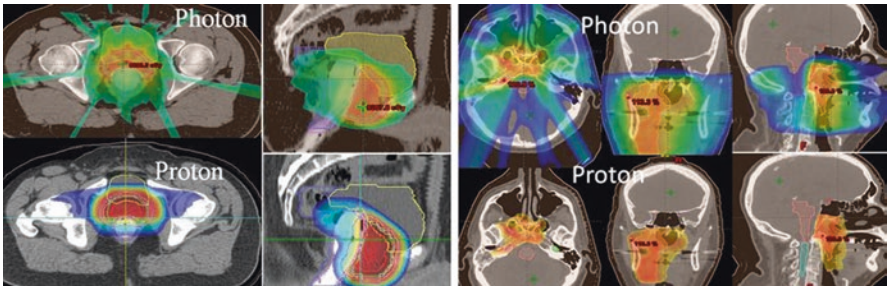

Fig. 18.7 Dose distribution comparison between photon, IMRT, and proton beam. Left panel is prostate and right panel is nasopharynx, indicating superior dose distribution with proton beam. The color wash is 30% isodose in both cases

Protons gain energy with each polarity change.
Goal is typically to gain several million electron-volts energy.
Modern machines can often reach energies of 250 MeV.
As protons gain energy, they gain mass due to relativity and may get out of sync and therefore cannot be accelerated further (Fig. 18.8).

– Synchrocyclotron
The RF field and magnetic fields can vary from the center of the Ds outward to compensate for relativistic effects as the particles approach the speed of light.

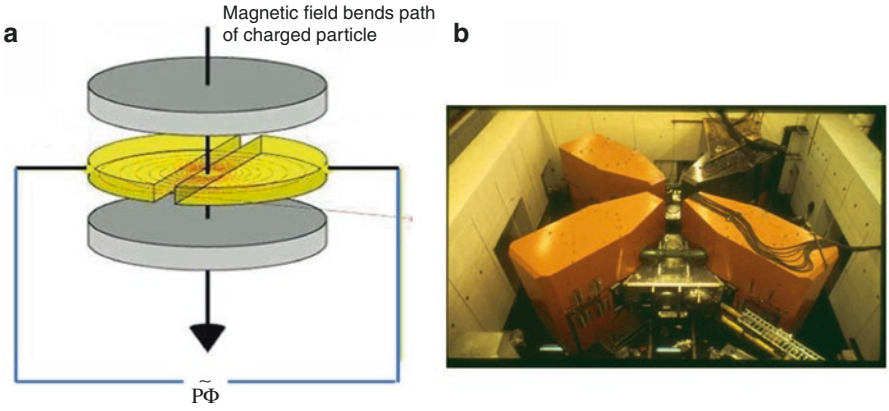

Fig. 18.8 (**a**) Schematic diagram of the cyclotron showing Ds, magnetic field, and RF power and (**b**) actual cyclotron from Indiana University Cyclotron Facility showing the horse-shoe electromagnet, Ds and RF power

Fig. 18.9 (**a**) A section of 96-meter diameter synchrotron from Hyogo Ion Beam (Japan) and (**b**) a section of synchrotron from Heidelberg Ion beam (Germany)

– Synchrotron
  A series of focusing and bending magnets operate in a powerful RF frequency that changes in stages, optimized with the speed, mass, and relativistic effects of the desired particle (see Fig. 18.9).
  Example: CERN supercollider which is a 40-kilometer diameter synchrotron.
  Synchrotrons can accelerate any charged particle, unlike cyclotrons which are limited to proton beams.

Clinical Proton Beam

- **Double Scattering**
  – Proton beam that leaves cyclotron/synchrotron is a narrow pencil beam (can travel in steel pipes guided by magnets as desired).
  – Snout: limits the beam coming out of the machine and contains a scattering foil (Fig. 18.11a).

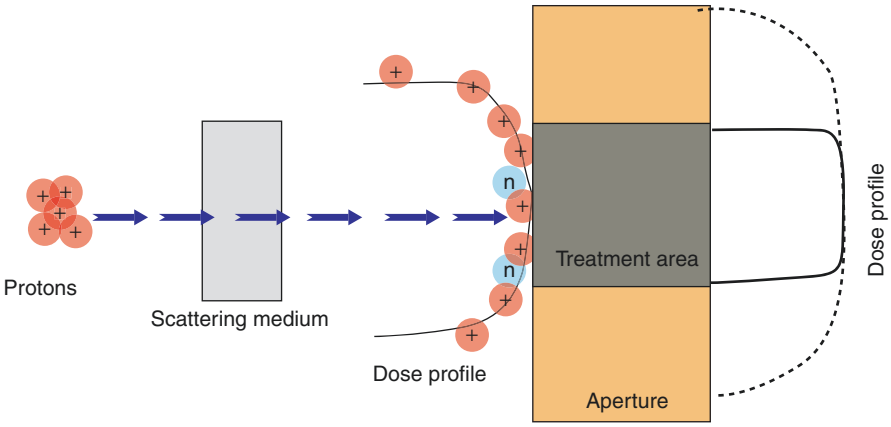

Fig. 18.10 Concept of beam scattering for making broad beam for patient treatment. The scattering medium creates broad beam with some neutrons. A cutout hole allows the proton beam to pass that has uniform dose profile

Similar to electron cones but MUCH bigger!
In order to be clinically useful, beam is broadened by placing a high atomic number medium in the path to scatter the beam (see Fig. 18.10).
This creates some neutron contamination.
This method is older and simpler than newer techniques.

– Aperture: final cross-sectional shape at the beam end, typically made of brass (Fig. 18.11b).
Apertures are typically unique for each field.
Apertures are typically made with a milling machine (in house or shipped out).
As protons are stopped in the aperture, they cause the aperture material to become radioactive (usually with short-lived positron-emitting isotopes).
Used apertures must be stored as radioactive material.
– Compensator: creates the three-dimensional profile of the target in the z-axis (Fig. 18.11c).
Typically milled from lucite, a type of plastic.
Unique for each field.
Also become radioactive after use (similar to aperture) (Fig. 18.11).

• Pencil Beam Scanning
– Pencil beam is broadened by a magnetic sweeping pattern over a target instead of a physical scattering device (see Fig. 18.12).
More uniform beam distribution possible.
Beam is typically scanned in layers in the x/y plane.
Range shifters can be inserted to add layers in the z plane.
If scanning is used uniformly for the entire flat plane (e.g., retrofit of an older scattering beam), then an aperture and compensators are still needed (expensive).

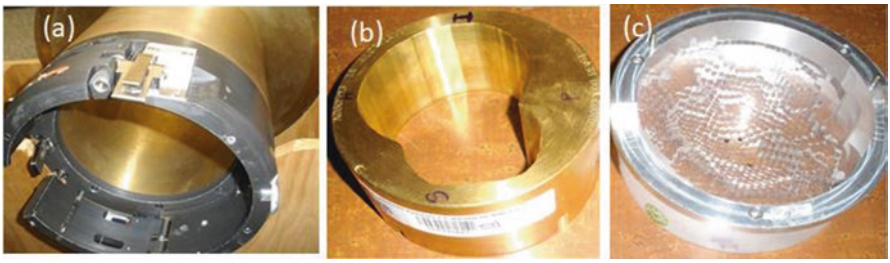

Fig. 18.11 Components of the double scattering proton beam head. (**a**) Snout that is placed in the nozzle. There is only limited number of snouts in a department; (**b**) brass aperture which is milled to reflect the BEV of a treatment area, (**c**) tumor-specific compensator for a BEV. The combination of aperture and compensator provides uniform dose to target and no dose beyond range to any normal structures

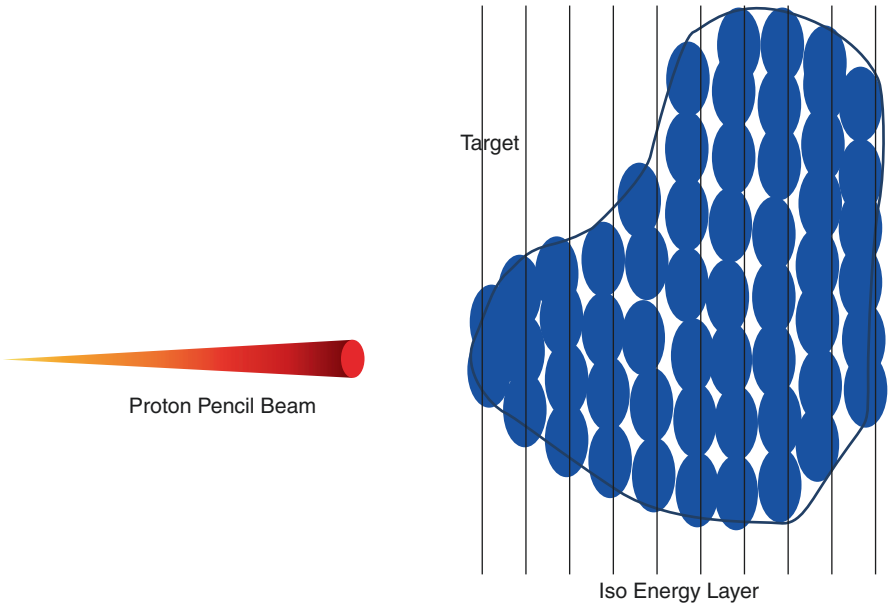

Fig. 18.12 The farthest layer is scanned using special two-dimensional magnet for scanning proton in x and y plane. The frequency of scanning is optimized for uniform dose distribution needed for lower and higher dose (depending on monitor unit) needed for patient treatment. As discussed earlier the z plane is range which is changed by adding a range shifter. So with the combination of x–y magnet and range shifter entire three-dimension of the tumor is covered. In such processes, however, the use of BEV aperture and compensators is needed

– IMPT (intensity-modulated proton therapy).
  Newer pencil beam scanning systems use magnets to create the shape of each layer in the x/y plane.
  Each new layer is created with a quickly shifting range shifter.

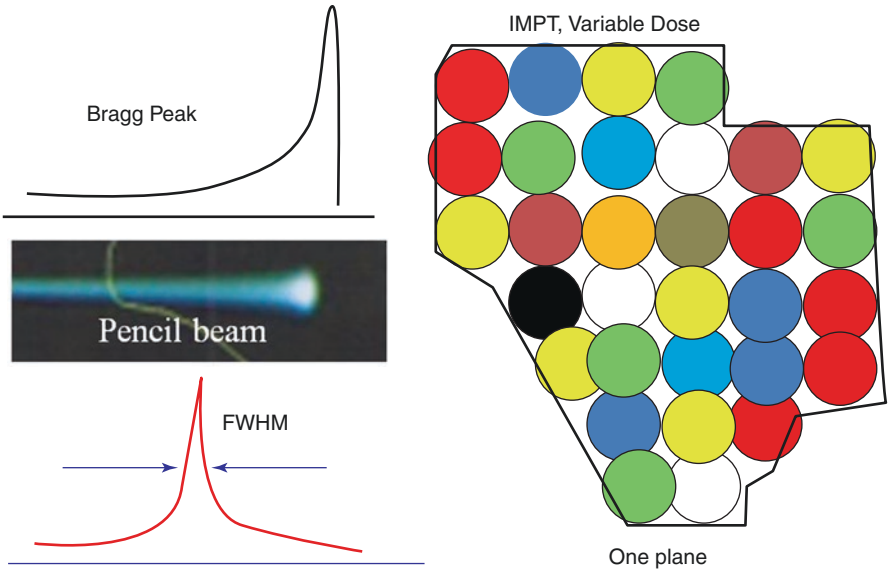

Fig. 18.13 A simplistic concept of pencil beam, indicating Bragg peak and full-width half maximum (FWHM). Pencil beam is prerequisite for IMPT where different dose is deposited shown by different colored dot

Far superior to double scattering or even retrofitted pencil beam scanning systems.

Size of pencil beam is critical and is governed by the full width at half maximum (FWHM) of the beam profile.

- Pencil beam size of 3–5 mm in air increases significantly as it enters the body, where there is no control or focusing mechanism. See Fig. 18.13.

Part II

Radiation Therapy Biology

Molecular Biology and Signaling

19

Introduction

The target of radiation for the purpose of therapy is the DNA. DNA is made up of sugars, phosphates, and bases and will form superstructures with other proteins to form chromosomes, which can be viewed under a microscope in the M-phase. Within the chromosome are genes that may be transcribed into proteins. The function of these genes can be altered by mutations or by epigenetic changes in expression. The RNA expression of genes can be visualized and measured through gene expression array profiling, hierarchical clustering, quantitative RT-PCR, and single-cell RNAseq. RNA levels can be regulated by transcription and microRNAs. Once translated, cells can regulate protein activity by: translocation; modifications such as phosphorylation and methylation; and degradation by the proteasome after ubiquitination. Signaling in cells has been found to be linked to various signal transduction pathways whose proteins regulate cell growth, cell cycle control, cell division, and cell death. These proteins can be cell surface receptors, ligands that bind cell surface receptors, intermediary signaling proteins, and activators such as transcription factors, apoptotic proteins such as BCL2 or BAX proteins. Radiation may cause several different kinds of cell death, which combine with various mediators and pathways to display the clinically evident acute and late effects of radiation.

A Note on Nucleic Acids (DNA)

- As a radiation biology text, this book focuses mostly on DNA and genes.
  - Information flows as follows: DNA → RNA → protein. This can also be described as gene → transcript → gene product.
- DNA is composed of sugars, phosphates, and bases. The sequence of bases carries the information (code).
  - **Purines** (**A**, **G**) pair with **pyrimidines** (**T**, **C**).

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https://doi.org/10.1007/978-3-030-61899-5_19

  - Purines are large while pyrimidines are small.
    "Big man, small name."
- DNA is wrapped around histones to form **chromatin**. Chromatin is the basic building block of **chromosomes**.
  - When talking about "single strand," "double strand," "chromatid," and "chromosome," it is easy to become confused because so many structures come in pairs (see Fig. 19.1).
- Unreplicated chromosomes (Pre-S) exist as a p- and q-chromatid, with no sister chromatids.
- Because humans are diploid, there are two of each chromosome.
  - However, unless you are a clone your two Chromosome 4′s are different from each other: One comes from your mom, the other comes from your dad.
- Replicated chromosomes (Post-S) exist as identical sister chromatids, bound together by a centromere.
  - You still only have one maternal chromosome 4 and one paternal 4, but each one has 2 p-arms and 2 q-arms.
- We are used to seeing replicated chromosomes because only **M-phase chromosomes** are visible in a traditional karyotype (light microscopy) (see Fig. 19.2).

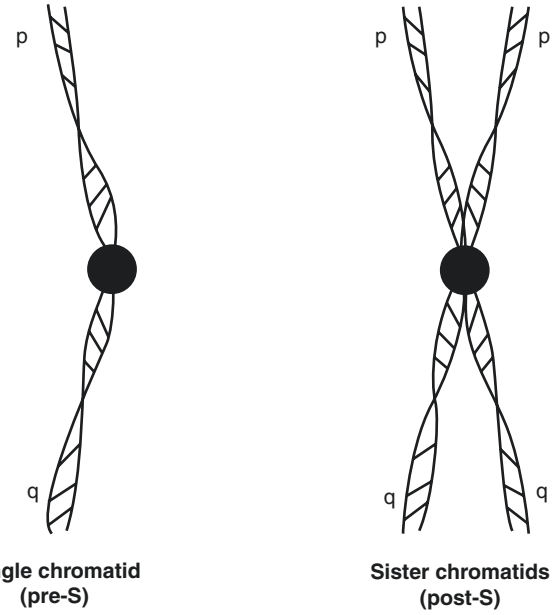

Fig. 19.1 A chromosome may contain one or two copies of each chromatid, but DNA is always double stranded

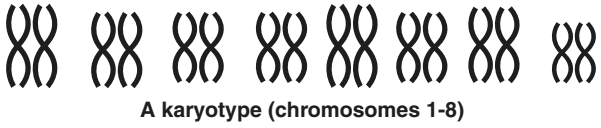

Fig. 19.2 DNA in a (partial) karyotype. Most of the cells in our body are not in M phase and do not have condensed chromosomes visible

A Note on Gene Function

- There are several ways to change the function of a gene. You can change the gene itself (**mutation**), you can change gene function without altering the gene (**epigenetic change**), or you can change the function of the gene product (protein).
- **Mutation** is pretty straightforward: The DNA is different so it behaves differently.
- **Epigenetic changes** are changes in gene function that do not alter the gene itself.
  - **Gene Expression**: Changes in the amount of mRNA transcribed from the gene.
  - **Splice Variants**: Changes in which parts of the gene are included in the final mRNA.

Point Mutations and Chromosomal Mutations

- **Mutations** may be classified by size:
  - **Point mutations**: 1 to a few bp in size.
  - **Gross mutations** (thousands to millions of bp).
  - **Aneuploidy** (whole chromosomes, tens to hundreds of millions of bp).
- **Point mutations** affect one or a few base pairs.
  - Single nucleotide mutations are also called single nucleotide polymorphisms (**SNP**) (see Fig. 19.3).
  - Mutations in coding regions are classified as **silent**, **missense, or nonsense mutations** (see Fig. 19.4).
  - Mutations in non-coding regions may affect the expression and splicing of coding regions, but they are not as easy to describe.
  - **Small Insertions and Deletions** (a few base pairs) also count as point mutations.

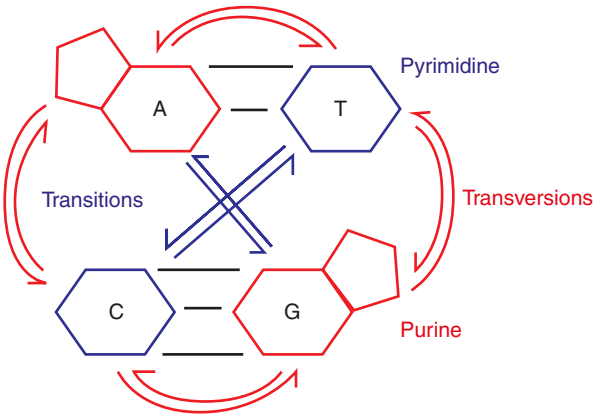

Fig. 19.3 Point mutations are classified as transitions (purine to purine or pyrimidine to pyrimidine) and transversions (purine to pyrimidine)

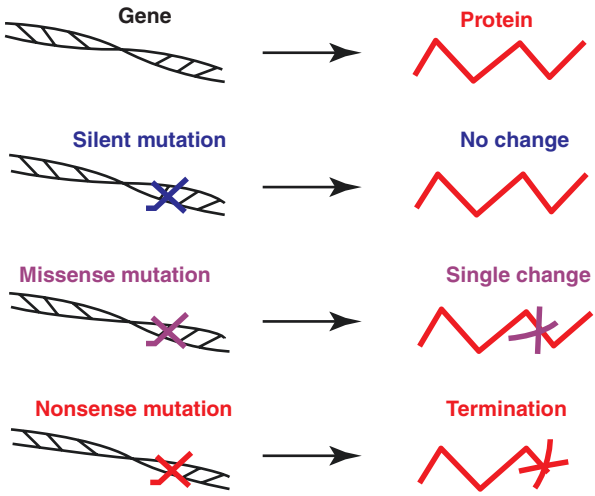

Fig. 19.4 Point mutations in a coding region of a gene may also be classified based on the change in the protein (gene product)

These occur when DNA replication "stutters" and either skips or repeats a sequence.

- **Chromosomal Mutations** (aka **gross mutations**) are large enough to affect the structure of an entire chromosome, generally millions of base pairs in length.
  - **Gross deletions** occur when pieces of DNA break off of the chromosome and are permanently lost.
  - **Translocations** occur when broken DNA sequences are re-attached to the wrong chromosome.
  - **Amplifications** occur when a DNA sequence is replicated multiple times in the same cell cycle.
- **Aneuploidy** is the loss or gain of entire chromosomes.
  - The normal human cell has two pairs of chromosomes 1–22 and two sex chromosomes (X, Y male or X, X female), i.e., **46XX** or **46XY**, anything different from this is aneuploidy (except for germ cells).
  - Aneuploidy happens when chromosomes fail to divide properly during mitosis.

    Most of these cells die (mitotic catastrophe) but surviving ones become aneuploid.
  - **Hypodiploidy** is having less than 46 chromosomes.
  - **Hyperdiploidy** is having more than 46 chromosomes.
  - **Tetraploidy** is having exactly twice the normal number of chromosomes (92). This happens after **cell fusion**.

Loss of Heterozygosity

- Humans have two copies of each chromosome and therefore each gene. This provides protection against recessive mutations. Even with one copy mutated, the healthy copy of a gene can take over its function.

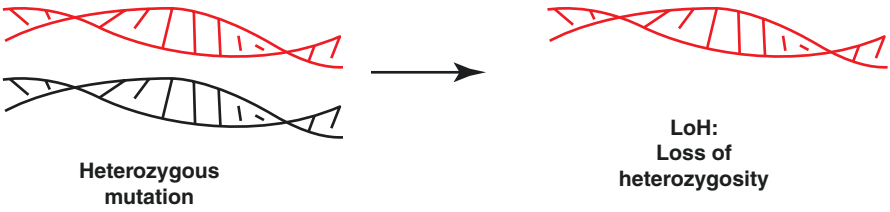

Fig. 19.5 Loss of heterozygosity (*LoH*) occurs when a gene is nonfunctional on both the maternal and paternal chromosome

  - A cell or individual carrying a recessive mutation is **heterozygous** at that locus (See Fig. 19.5).
- **Loss of heterozygosity** (**LoH**) is used to describe any gene locus that is mutated and/or lost on both chromosomes.
  - This is a "two-hit" mechanism of mutation. One chromosome is defective for a long time (possibly inherited), while the other chromosome is newly deleted.

Gene Expression

- Most of the cells in your body have the same genome, yet a skin cell acts very different from a brain cell.
- How does a cell regulate its gene function without changing its genome?
- **Increased Gene Expression**:
  - **Positive Transcription Factors**: Signaling proteins may directly bind DNA to induce or suppress transcription.
  - **Chromatin Acetylation**: Opens up chromatin and induces gene expression.
- **Decreased Gene Expression**:
  - **Negative Transcription Factors** (**Repressors**).
  - **Chromatin Methylation**: Closes down chromatin and prevents gene expression (see Fig. 19.6).
- **Transcript** (**mRNA**) **modification**:
  - Many human genes have multiple splice variants, so that one gene can produce different gene products.
- **Overexpression** and **Silencing** describe an overall increase or decrease in gene expression. These terms include both mutation (gene amplification or deletion) and epigenetic changes.
- **MicroRNA** (***mi*RNA**) **regulation of mRNA levels and protein translation.**
  - Cells synthesize and use small endogenous, non-coding ***mi*RNAs** to alter mRNA levels post-transcriptionally and therefore also protein translation levels.
  - **miRNA** levels are altered in many cancers by amplifications, deletions, and transcriptional misregulation.
  - For example, ***mi*R-15a** and ***mi*R-16-1** have been found to be deleted in B-cell lymphocytic leukemias, and ***mi*R-143** and ***mi*R-145** are deleted in lung cancer and are considered tumor suppressors.

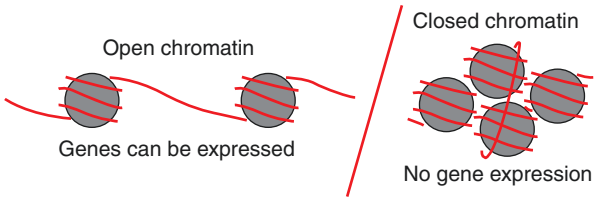

Fig. 19.6 Chromatin may exist in a "closed" (inactive) state or an "open" (active) state. This is regulated by acetylation and methylation

- By contrast, the ***mi*R-17-92 cluster** which encodes several individual ***mi*RNAs** is overexpressed in several lymphomas and in lung, colon, and liver cancers, and is considered oncogenic.
- Radiation can alter ***mi*RNA** levels and depending on cell type and radiation dose can be induced or repressed.
- The EGFR receptor and PI3K/AKT is a prosurvival pathway involved in the radiation response and is regulated by several miRNAs such as the ***mi*R-302-367 cluster** and ***mi*R-7.** PTEN, an AKT negative regulator, is regulated by ***mi*R-21**.

Post-translational Modification

- Once a gene has produced a protein that has properly folded after translation, a protein's function and activity are frequently regulated by other processes/modifications (see below) within the cell.
- **Protein modification**:
  - Phosphorylation/dephosphorylation.
  - Hydroxylation.
  - Dimerization.
  - Crosslinking.
- **Changes in protein lifetime**:
  - Ubiquitination: The small protein ubiquitin "tags" a protein for degradation by the **proteasome** (the cell's "garbage collector").
- **Translocation: Change in protein location, for example, between the following organelles**:
  - Cytoplasm.
  - Nucleus.
  - Plasma membrane.
  - Mitochondrion.
  - Endoplasmic reticulum.
  - Other organelles.

Phosphorylation and Dephosphorylation Reactions

- Phosphate groups are the most common high-energy chemical group in the cell. Therefore, **phosphorylation/dephosphorylation** is a common mechanism for modification of protein function (and can act like an "on/off switch").

  - **Kinases** add phosphate.
  - **Phosphorylases** remove phosphate.
- Serine, threonine, and tyrosine amino acid residues can bind phosphate.
- Kinases and phosphorylases are classified by the amino acid they are capable of acting on.
  - Tyrosine kinases (**TKs**) include all of the growth factor receptors.
    EGFR, **Her2/Neu**, **PDGFR**, **VEGFR**, **IGFR**.
  - Serine/threonine kinases
    MAPK, **ERK**, **TGFβR**.

Molecular Signaling: Receptors and Ligands

- **Receptors** are classified based on their location and function:
- **Membrane-bound receptors** bind **ligands** located outside the cell.
  - Ion channel-type receptors can selectively allow ions or other small molecules to flow in or out of the cell.
  - Receptor kinases work through phosphorylation, including all of the growth factor receptors.
  - G-protein-coupled receptors (**GPCRs**) require GTP-binding proteins (G-proteins) to work. Most GPCRs are also receptor tyrosine kinases.
- **Cytoplasmic signaling molecules** transmit information from membrane-bound receptors to the nucleus.
- **Transcription factors** bind DNA, directly altering gene expression.
  - **Nuclear receptors** are transcription factors that can directly respond to specific ligands.
  - Transcription factors may be held in the cytoplasm where they are inactive. In response to a signal, they translocate into the nucleus where they can bind to gene promoters in the DNA.
  - NF-κB is a heterodimer of p65/p50 that is an example of a transcription factor that is kept in the cytoplasm by binding to the protein inhibitor of kappa-beta (Iκ-B) until it receives upstream signaling that releases the Iκ-B from Iκ-B/NF-κB complex and allows NF-κB transcription factor to enter the nucleus and induce transcription of NF-κB-regulated genes.
- **Ligands** are classified into several types:
  - **Water-soluble ligands** cannot pass through the cell membrane without a specific transport channel. These include neurotransmitters, growth factors, antibodies, and most nutrients and metabolites.
  - **Lipid-soluble ligands** can freely travel through the cell membrane. This includes the steroid hormones and thyroid hormone, as well as lipid-soluble metabolites.
  - **Membrane-bound ligands** are molecules expressed on the surface of other cells, such as the **MHC** groups responsible for T-cell-mediated immunity.

Gene Expression Profiling

- A **multi-gene array** ("gene chip") can measure numerous genes at the same time:
  - **mRNA** is harvested from a tissue sample (normal tissue, tumor, experimental animal, cell culture).
  - **mRNA** is converted into complementary DNA (**cDNA**) by reverse transcriptase.
    RNA is too unstable to use directly because of the ubiquitous presence of RNAses (enzymes that degrade RNAs) in cells, tissue, and the environment. **cDNA** is also known as the "transcriptome."
  - **cDNA** is labeled with a fluorescent dye and placed on a library of known DNA sequences.
  - Fluorescence is measured by laser scanning.
- By using **cDNA** derived from two different tissue samples, one labeled green, one red, you can compare gene expression "at a glance."
  - Control is green and experimental is red.
  - Therefore, red gene sequences are overexpressed and green gene sequences are underexpressed (see Fig. 19.7).
- **Hierarchical clustering (HC)** of **gene expression array (GCA)** data is a statistical method that allows researchers to cluster gene expression patterns into groups/cell types.
  - For example, **HC** and **GCA** can be used to identify the four genetic subtypes of breast cancer: "Luminal A," "Luminal B," "Her2," and "Basal-like."
  - **HC** and **GCA** can also identify various subsets of normal cells in tissues in various organs and tumors. For example, immune cell subtypes (B cells, T cells, macrophages, etc.) can be identified in lymph nodes and tumors.

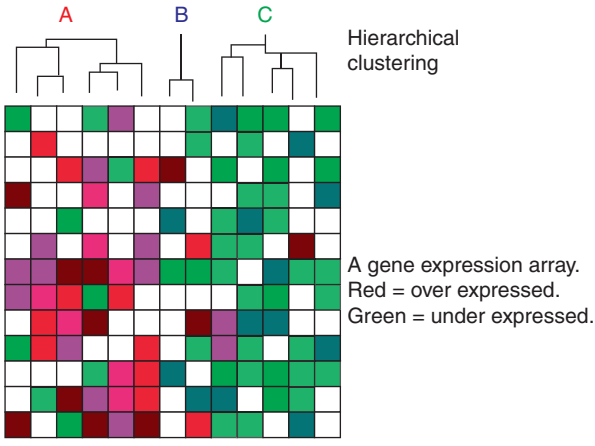

Fig. 19.7 Gene expression arrays can show the relative expression of up to thousands of target genes at once. Cluster analysis can then be used to group genes together to fit a specific pattern. A, B, and C are arbitrary labels for "clusters" of similar specimens

Single-Cell RNAseq (scRNAseq)

- Deep cDNA sequencing and big data clustering analysis of the transcriptome of individual cells by **single-cell RNAseq (scRNAseq)** has allowed the identification and quantitation of small, complex subpopulations of cell types in normal tissues and tumors including tumor and normal tissue stem cells.
  - **scRNAseq** analysis of tumors before and after treatment has the potential to identify sensitive and resistant cell subtypes in tumors and in the future may help guide treatment.

Types of Cell Death

- There are several ways in which cell death may occur:
- **Necrosis** is typically unorganized and provokes an inflammatory response by loss of cell integrity.
- **Apoptosis** is organized, planned cell death that does not provoke an inflammatory response.
- Cells with lethal DNA damage may not die until they attempt to divide and fail mitosis. This is called **mitotic catastrophe**.
- For more details, see Chap. 22.

Radiation-Induced Molecular Signals

- Cells may respond to ionizing radiation in several ways. Often times, different responses compete against one another.
- **DNA Repair**: Activation of molecular systems to repair the DNA damage caused by radiation.
- **Cell Cycle Arrest**: Prevents the cell from cycling with damaged DNA. Can promote repair and survival, but slows down cell growth.
- **Apoptosis**: Programmed cell death, removes damaged cells from the body. Not all tissues undergo apoptosis, and many cancer cells are apoptosis-deficient.
- **Proliferation**: The opposite of cell cycle arrest and apoptosis. Produces new cells to compensate for cell killing.
- **Inflammation**: Increased blood flow and immune system activity as a result of cytokine induction, causes some cells to grow (proliferation) and other cells to die (apoptosis or necrosis).
- **Fibrosis**: Production of scar-like extracellular stroma, common late toxicity of irradiation.

Acute Effects: DNA Damage

- DNA damage is detected by the proteins **ATM/ATR**.
- When a cell recognizes that it is damaged, a repair-proficient cell will attempt to repair the damage. At the same time, it must decide how it will react to this damage.
  - See Chap. 21 for details on DNA repair.
- The cell may decide to stop growing and even kill itself (apoptosis) if too badly damaged.
  - **p53 pathway**: A protein that is pro-repair, pro-arrest, and pro-apoptosis.
  - **Ceramide pathways**: Ceramide is a lipid that is pro-arrest and pro-apoptosis.
  - "Arrest and death" pathways tend to prevent malignancy as they prevent mutated cells from proliferating.
  - However, cell loss in normal tissues can lead to loss of function.
- Or the cell may decide to proliferate and survive, compensating for damage by growing faster.
  - **Fos/jun/myc pathway**: Pro-growth and anti-apoptosis.
  - "Survival and growth" pathways can predispose to malignancy as they allow mutated cells to grow.
  - However, they are also responsible for re-populating normal tissues after an injury.

Late Effects: Inflammation and Fibrosis

- Wounds leave scars … and so does radiation!
- Inflammation is a normal response to injury and can help to fight infection.
  - Increased blood flow.
  - Enhanced immune response.
  - Increased cell turnover: both cell death and proliferation are increased.
- Later on, fibrosis (hardening of the tissue) occurs.
  - Increased production of scar-like extracellular matrix.
- **TNFα**, **TGFβ**, **PDGF**, **FGF**, and **IL-1** are inflammatory mediators that may also play a role in fibrosis.

Check for updates

Cancer Biology

20

Introduction

Cancer results from an accumulation of multiple mutations in cellular genes that regulate cell growth/life span, death, and migration, immune response, telomere length, genomic instability, invasion, and metastasis. Some mutations are inherited while most others are spontaneous or induced. Mutations may increase the activity of oncogenes or decrease the activity of tumor suppressors. The various steps in evolution from a normal cell to a cancer cell may be classified as initiation, promotion, and progression. Cancer cells must develop the ability to divide uncontrolled while maintaining their telomere length, recruit vasculature through VEGF, and alter cell-cell adhesion to invade and metastasize. Better understanding of tumor genetics has led to targeted cancer therapy, with monoclonal antibodies and small molecule inhibitors directed at specific molecules and molecular pathways dysregulated in human cancers.

Genetic Changes in Cancer

- Analysis of cancer cells shows that most of them have highly abnormal DNA, with multiple changes compared to healthy cells.
- As discussed in Chap. 19, many different types of mutations may occur.
- Mutations occur through several mechanisms:
  - **Heritable**: Present at birth.
    BRCA1/2 mutations cause heritable breast/ovarian cancer.
    FAP and MSH/MLH mutations cause heritable colon cancer.
    Rb mutations cause heritable retinoblastoma and soft tissue sarcomas.
    p53 mutations cause Li-Fraumeni syndrome, with multiple malignancies.
  - **Spontaneous**: Random mutations due to aging, oxidation, and the process of DNA replication and mitosis. Large-scale DNA sequencing of many human

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cancers has shown that the majority of the mutations that drive the carcinogenic processes appear to be spontaneous.

Genomic instability: Loss of DNA repair, cell death processes such as apoptosis, and senescence pathways lead to accumulation of spontaneous mutations over time.

  - **Chemical induced**: Many chemicals (tobacco smoke, etc.) cause base damage or DNA crosslinks, and are more likely to cause point mutations.
  - **Radiation induced**: Radiation causes double-strand breaks and is more likely to cause gross mutations.
  - **Cell fusion**: Two cells combine into one, doubling DNA content (tetraploidy) and increasing the rate of mutation.
- Abnormal genes may also be introduced by a virus:
  - **HPV** (human papillomavirus) is the widely publicized virus responsible for cervical cancers and some head and neck cancers. The HPV E6 protein targets the p53 tumor suppressor protein for degradation which disrupts cell cycle checkpoint control and cell death processes such as apoptosis. The HPV E7 protein targets the retinoblastoma (Rb) protein and disrupts normal cell cycle progression and control.
  - **EBV** (Epstein-Barr virus), also known as human herpesvirus 4, causes mononucleosis and is responsible for nasopharyngeal cancers in China and Southeast Asia and Burkitt's lymphoma in Africa. EBV latent membrane proteins (LMP_1 and LMP) and EBV nuclear antigens disrupt cellular signaling in proliferation, metastasis, and cell death such as apoptosis.

Epigenetic Changes in Cancer

- As described in Chap. 19, epigenetic changes are changes in gene function without any change in the gene itself.
- The most common epigenetic change is chromatin modification.
  - **Methylation** decreases gene expression.
  - **Acetylation** increases gene expression.
- Hyper-methylation of gene promoters is the most common form of **epigenetic silencing**.
  - Cancer cells use methylation to turn off tumor suppressor and DNA repair genes. This may leave them vulnerable to DNA damaging agents (chemo, radiation).
  - **MGMT methylation** in glioblastoma correlates with response to **temozolomide**.

Multistep Model of Carcinogenesis

- Cancer is a disease of uncontrolled proliferation, invasion, metastasis, angiogenesis, and immune avoidance. It usually takes many changes to turn a normal cell into a cancer cell.
  - A cell with uncontrolled proliferation but no invasion or metastasis may form a tumor, but it is likely to be benign or premalignant.

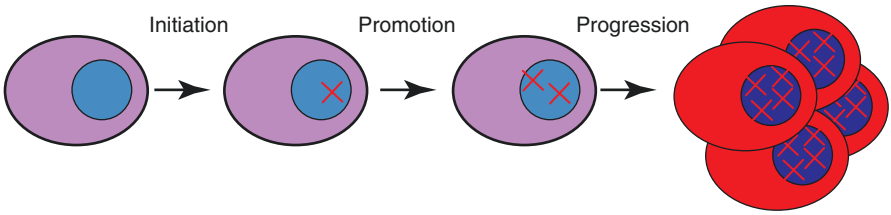

Fig. 20.1 Multiple mutations are required to turn a normal cell into a cancer cell. These are referred to as initiation, promotion, and progression

  - For example, genital warts are typically benign, but with high-risk HPV such as HPV16 and 18 subtypes they may become malignant.
- **Initiation** is the first mutation(s) that promotes uncontrolled proliferation.
- **Promotion** is a second mutation(s) that has little effect in a normal cell, but after **initiation** can cause a further increase in proliferation.
- **Progression** can lead to additional mutations that confer malignant characteristics such as invasion and metastasis (see Fig. 20.1).
- Genetic analysis of benign, premalignant, and malignant tumors shows that mutations frequently happen in a specific order:
  - For example, **APC** and **K-Ras** are commonly mutated in benign colon adenomas (initiation).
  - **CIN** and **DCC** are commonly mutated in dysplastic colon adenomas (promotion).
  - **p53** is commonly mutated in invasive colon cancer (progression).

Clinical Significance of Cancer Genomics

- Gene profiling technologies have allowed for measurement of gene expression in human tumors; this is increasingly used for prognostic and therapeutic decision-making.
- **Cytotoxic therapy** (classical chemotherapy) damages DNA or inhibits metabolic pathways common to many human cells.
  - Genomics may be used to predict efficacy and toxicity of cytotoxic drugs.
- **Targeted therapy** is designed to specifically inhibit certain cell signaling pathways.
  - Genomics may be used to identify specific mutations or molecular pathways that can be targeted by drugs.
  - Not all targeted therapies target oncogenes.
- **Prognostic gene panels** attempt to predict tumor behavior and treatment response.
  - The **Oncotype DX** multi-gene panel is used to predict the utility of chemotherapy in early-stage invasive breast cancer.
  - The **Oncotype DCIS** multi-gene panel may predict the utility of whole-breast irradiation in DCIS.

Oncogenes and Tumor Suppressors

- An **oncogene** ("tumor gene") is a gene that encourages tumor formation.
  - Oncogenes may act through one of the following:
    Encouraging proliferation.
    Encouraging survival (anti-apoptosis).
    Deactivating tumor suppressors.
  - Oncogenes may become activated through mutation, amplification, or overexpression.
- A **proto-oncogene** is the normally functioning version of an oncogene.
  - For example, normal b-Raf is a **proto-oncogene**, and mutant b-Raf is an **oncogene**.
- A **tumor suppressor** is a gene that can prevent tumor formation.
  - Tumor suppressors may act through one of the following:
    Promoting cell cycle arrest.
    Promoting apoptosis.
    Promoting DNA repair.
    Inhibiting oncogenes.
    Rb and **p53** can both cause **G_1 arrest.**
    p53 can also cause **G_2 arrest**.
  - Tumor suppressors may become deactivated through **mutation** or **epigenetic silencing**.
  - Tumor suppressors may also have a pro-apoptotic function.
    Rb and **p53** are both pro-apoptotic and pro-arrest.
  - Tumor suppressors may act by inhibiting oncogenes.
    NF1 (neurofibromatosis type 1 gene) inhibits **Ras**.
  - Tumor suppressors may be DNA repair genes.
    BRCA1/2 and **MLH/MSH** are DNA repair genes that strongly predispose to cancer if damaged/mutated.

Principles of Targeted Therapy

- It is much easier to inhibit an overactive oncogene than to restore a silenced tumor suppressor gene.
- Monoclonal antibody-based drugs (**−mabs**) are very large and cannot easily cross cell membranes. Therefore, their targets are limited to cell-membrane receptors and ligands.
  - Antibodies are very specific for one target molecule, and have difficulty crossing the blood-brain barrier.
- Small molecule inhibitor drugs (**−ibs**) can cross cell membranes and target either extracellular or intracellular targets.
  - Tyrosine kinase inhibitors (**TKI**s) may or may not cross the blood-brain barrier.
  - Most **TKI** drugs inhibit multiple tyrosine kinases at the same time.

The EGFR-MAPK Signaling Pathway

- This is a pro-growth and pro-survival signaling pathway that contains many clinically relevant drug targets (Fig. 20.2).
- **The EGFR family**: These tyrosine kinase receptors sit in the cell membrane and receive growth and stress-related signals including **EGF** and are frequently mutated in cancer.
  - **EGFR (ErbB, Her1)**: Implicated in squamous cell cancers, targeted by drugs including cetuximab, panitumumab, erlotinib, and gefitinib.
  - **HER2/neu (EGFR2, ErbB2)**: Implicated in breast cancers, targeted by drugs including trastuzumab, pertuzumab, and lapatinib.
  - **EGFR3** and **EGFR4** also exist.
- **Ras**: A membrane-bound "G-protein" (GTP binding protein) that transmits signal from EGFRs.
  - **K-Ras**: Commonly mutated at codon 12 (*KRAS G12C*) in colon, lung, and pancreatic cancers, activates *KRAS* and confers resistance to EGFR inhibitors. Inhibiting EGFR does nothing if the mutation is downstream of EGFR.
  - **H-Ras** and **N-Ras** also exist. H-Ras is mutated and activated in bladder and head and neck squamous cancers. Tipifarnib, a farnesyl transferase inhibitor, is being investigated in H-ras-mutated head and neck cancers. N-Ras is mutated in malignant melanomas and colorectal cancers.
- **Raf:** A cytoplasmic signaling protein that transmits signal from Ras.

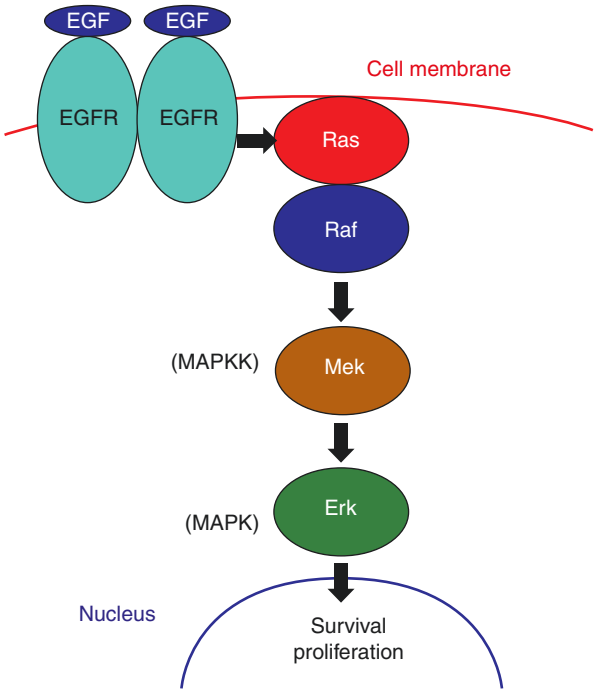

Fig. 20.2 An illustration of the EGFR-MAPK pathway

  - **b-Raf**: Commonly mutated in melanoma, renal, and liver cancers. Targeted by drugs including sorafenib and vemurafenib.
  - **a-Raf** and c-**Raf** also exist.
- **Mek (MAPKK, MAP 2 K)**: An intermediate signaling protein between Raf and Erk (MAPK).
  - Multiple subtypes exist.
- **Erk (MAPK)**: A signaling protein that activates pro-growth and pro-survival factors in the nucleus such as the AP-1 (Jun, Fos) transcription factor complex, and the STAT3/VEGF pathways that regulate angiogenesis (see below).
- Multiple subtypes exist.

Angiogenesis and VEGFR

- Angiogenesis is the growth of new blood vessels. This signaling pathway encourages angiogenesis and cell survival, both of which can help tumors grow.
- **VEGFR (Flt/Flk)**: These tyrosine kinase receptors sit in the cell membrane and receive angiogenesis signals from **VEGF**.
  - Multiple subtypes exist.
  - Targeted by drugs including bevacizumab, pazopanib, sunitinib, and sorafenib.

The PI3K-Akt-mTOR Pathway

- This series of signaling molecules is pro-angiogenesis, pro-growth, and anti-apoptosis. It may be activated by VEGFR, IGFR HIF1, and other upstream signals (see Fig. 20.3).
- **PI3K**: This membrane-bound protein manufactures PIP3, a signaling lipid implicated in both cancers and diabetes.
  - **PTEN** is a tumor suppressor that mainly inhibits PI3K.
- **Akt (PKB)**: A signaling protein that is closely associated with mTOR, and leads to pro-survival, anti-apoptotic pathways.
- **mTOR**: A signaling protein that is implicated in immune function, obesity, cancer, and various other processes.
  - Targeted by drugs including sirolimus (rapamycin), temsirolimus, and everolimus. These immunosuppressive drugs also have an anti-cancer effect in some kidney cancers and lymphomas.

Other Oncogene Drug Targets

- **BCR-ABL** and **c-kit** are pro-growth tyrosine kinases found in lymphomas and other cancers.
  - Targeted by the tyrosine kinase inhibitor imatinib.

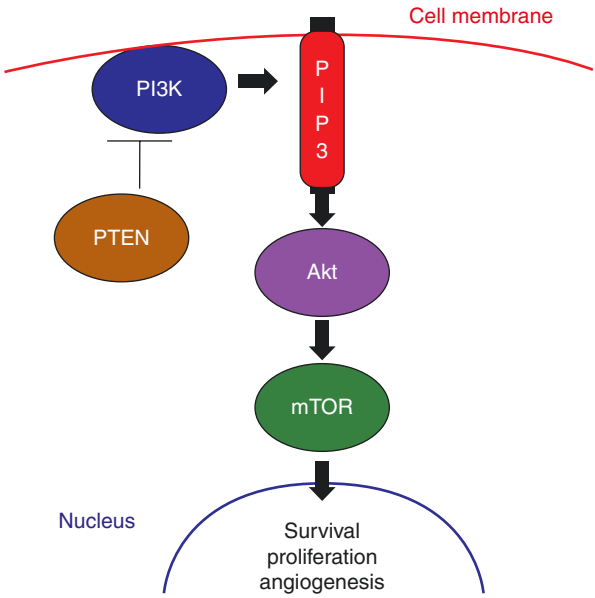

Fig. 20.3 An illustration of the PI3K-Akt-mTOR pathway

- **ALK** is a kinase found in some lung cancers and lymphomas.
  - Targeted by the ALK inhibitor crizotinib.
- Oncogenes may act by deactivating tumor suppressors.
  - **HPV E6** and **E7** deactivate **p53** and **Rb,** respectively, causing squamous cell cancers.
  - Oncogenes may act by preventing apoptosis.
    Bcl-2 and other anti-apoptotic genes are frequently overexpressed in tumors.

Oncogene Signaling and Radiation Therapy

- **p53** is mutated in roughly 50% of all human cancers and is greatly involved in the DNA damage response.
  - Cancer cells deficient in **p53** are deficient in RT-induced DNA repair, cell cycle arrest, and apoptosis.
    This may increase radiosensitivity in some cells due to loss of repair and cell cycle arrest.
    This may decrease radiosensitivity in some cells due to loss of apoptosis.
- **NF – κB** is a pro-survival and pro-inflammatory signaling molecule that is commonly overexpressed in cancer cells.
  - Tumors with normal levels of **NF – κB** are much more likely to undergo apoptosis in response to radiation therapy.
  - Tumors with **NF – κB overexpression** are highly resistant to radiation-induced apoptosis.

Invasion and Metastasis

- The genetic basis of invasion and metastasis is less well understood than proliferation.
- Invasion requires the loss of normal cell-cell adhesion and degradation of the normal extracellular matrix.
  - Deletion of **E-CAD** and **N-CAM** causes loss of adhesion.
  - Matrix metalloproteinases (**MMPs**) degrade cell matrix.
- Metastasis requires the ability of tumor cells to enter and exit blood or lymph vessels, and to thrive in a new environment.
  - Loss of apoptosis, increased survival, and growth signals.
  - "Seed and soil": certain cancers tend to metastasize to specific sites. For example, lung cancer makes brain mets, prostate cancer makes bone mets.

Quiescence and Senescence

- A cell that is normally capable of dividing may stop dividing for many reasons: extrinsic signaling, loss of nutrients, DNA damage, and so on.
- **Quiescence** is a reversible growth arrest but cells may resume proliferation at a later time. It is frequently induced when cells are exposed to suboptimal growth conditions (low nutrients, growth factors, very low oxygen levels).
- **Senescence** is a permanent growth arrest induced by aging, DNA damage, or other noxious stimuli (also see Chap. 22).
  - Permanent down-regulation of multiple growth factor pathways.
  - Expression of the cyclin-dependent kinase inhibitor 2A p16 or p16ink4A which inhibits cdk4 activity.
  - Expression of senescence-associated beta-galactosidase.

Telomeres and Cancer

- DNA in eukaryotic cells is linear, unlike in bacteria.
- Problems with **linear DNA** include:
  - **Sticky ends** – unwanted end-to-end joining leads to mutations and anaphase bridges.
  - **Cannot be completely replicated** – a small amount of DNA on each end is lost with each replication cycle.
- **Telomeres** are repetitive DNA sequences that cap both ends of the chromosome and prevent sticking.
  - A small amount of telomere is lost with each replication cycle.
  - As cells age their telomeres shorten until the cell becomes senescent.

    The number of divisions a normal cell can undergo before senescence is known as the **Hayflick limit**.

- **Telomerase** allows cells to regenerate telomeres:
  - Most normal cells do not express telomerase.
  - Immortal stem cells and germ cells do.
  - Cancer cells must express telomerase or telomerase-like activity to maintain their ability to proliferate (see Fig. 20.4).
- **Breakage-fusion-bridge** (**BFB**) **hypothesis**: Cells that try to divide despite insufficient telomere length undergo cycles of DNA breakage, fusion, and anaphase bridges.
  - This is known as "**crisis**" and is almost always lethal (mitotic catastrophe).
  - Surviving cells have grossly mutated DNA with multiple deletions, translocations, and aneuploidy.
  - A cell that survives crisis may reactivate telomerase and once again increase the length of the telomeres and escape from crisis.
  - It then resumes proliferation, propagating mutations to all of its daughter cells.
- **Hallmarks of Cancer**: Genetic and epigenetic changes that result in normal cells progressing to cancer have been summarized by Hanahan and Weinberg as "Hallmarks of Cancer."
- These hallmarks include:
  - Sustained growth signaling (activation of oncogenes Ras, Myc, cytokines).
  - Evasion of growth suppressors (silencing of tumor suppressor [TS] genes [RB, p16, p21, and p53]).
  - Activation of invasion and metastasis (activation of oncogenes and silencing TS genes, proteases, ECM, integrins).
  - Replicative immortality (activation of telomerase).

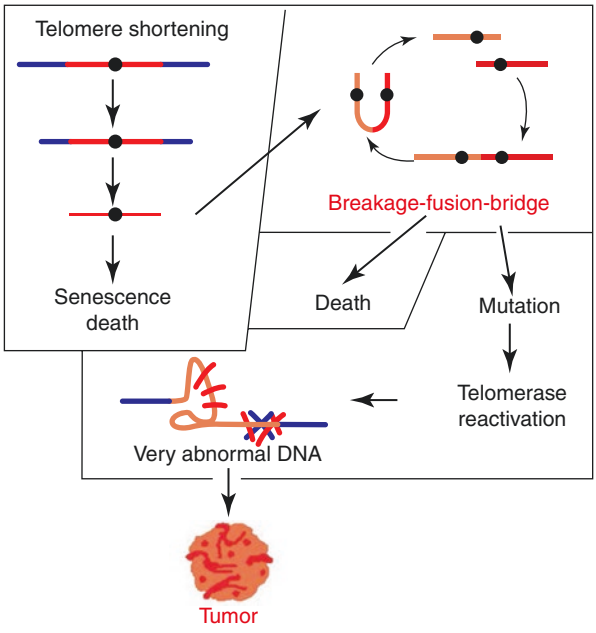

Fig. 20.4 Telomeres grow shorter with each cell cycle. When they are too short chromosomes become sticky, causing a "crisis" of breakage-fusion-bridge events. This usually causes cell death but may also lead to tumor formation

- Induction of angiogenesis (activation of VEGF).
- Resistance to cell death (activation of oncogenes [RAS], inhibition of TS genes [P53], and overexpression of anti-apoptotic genes [BCL-2]).
- Deregulation of cellular energetics (Warburg metabolism); activation of oncogenes (RAS, etc.).
- Avoidance of immune detection (PD-1, PD-L1, and CTLA-4 expression).
- Tumor inflammation (activation of TNF-α, and pro-inflammatory cytokines).
- Genomic instability (tolerance of DNA damage, ATM, p53, CHK1, and CHK2).

Molecular Mechanisms of DNA Damage and Repair

21

Introduction

There are many types of lesions that may be induced in DNA by ionizing radiation. Radiation creates ion pairs in water. If clusters of ionization are formed near DNA, they can potentially damage the DNA. Normal well-oxygenated cells may utilize various pathways to repair different types of DNA damage. Base damage and single-strand breaks (SSB) are usually easy for a cell to repair while double-strand breaks (DSB), which may be repaired by non-homologous end-joining (NHEJ) or homologous repair (HR) repair pathways, are more difficult. Unrepaired or mis-repaired DSBs can result in unstable chromosomal aberrations that can, in turn, lead to either death or senescence of the cell. The mechanisms of DNA repair are important to understand, not only in regard to radiation damage repair, but also because their absence or inhibition may play a role in the genetic predisposition to cancer or the response of tissues or tumors to ionizing radiation or DNA-damaging chemotherapy agents.

Types of DNA Damage

- Oxidation, chemotherapy, and radiation therapy can all damage DNA. There are many ways in which this can occur.
- **Base Damage**: A DNA base is chemically altered. This may cause a point mutation, or it may predispose to additional DNA damage.
- **Base Mismatch**: A mistake during DNA replication leads to insertion of the wrong base. This will cause a point mutation if it is not repaired.
- **Pyrimidine Dimers**: Two adjacent pyrimidine bases are cross-linked by ultraviolet light. This will cause a point mutation if it is not repaired prior to replication.
- **Intercalation**: This occurs when abnormal chemical groups (such as chemotherapy drugs) are interposed in the DNA helix. This may prevent gene function and replication.

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- **Crosslinking**: This occurs when abnormal chemical bonds are formed within the DNA molecule or between DNA and protein. This may prevent gene function and replication, or cause DNA-strand breaks.
- **Single-Strand Breaks (SSBs)**: The sugar backbone is broken on one strand but not the other. This is easily repaired as long as the other strand is still intact.
- **Double-Strand Breaks (DSBs)**: When the DNA is broken on both strands in identical regions across from each other or on opposite strands within a few base pairs of each other, a DSB may be formed. The ends at the breaks will be "sticky" and can react with other "sticky" broken DNA strands. This causes chromatid and chromosome aberrations that may be mutagenic or lethal.

Ionizing Radiation and DNA Damage

- Each **Gy** of ionizing radiation causes approximately:
  - >5000 × base damage
  - 1000 × SSBs
  - 40–50 × DSBs
- The DSB is the primary "mechanism" of cell killing after exposure to ionizing radiation. The number of DSBs correlates with cell killing, while the other types of damage do not.
  - In contrast, chemotherapy-induced DNA damage depends on the drug and may include base damage, intercalation, crosslinking, and DSBs (Fig. 21.1).

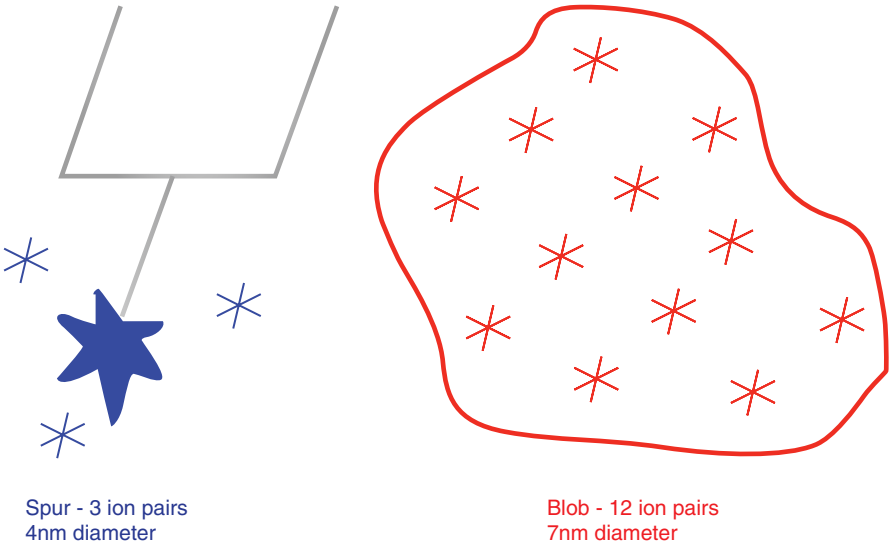

Fig. 21.1 Ionizing radiation can form clusters of ion pairs in water. "Spurs" contain 3 ion pairs across ~4 nm and predominate after exposure to low-LET irradiation. "Blobs" contain 12 ion pairs across ~7 nm and predominate after exposure to high-LET irradiation

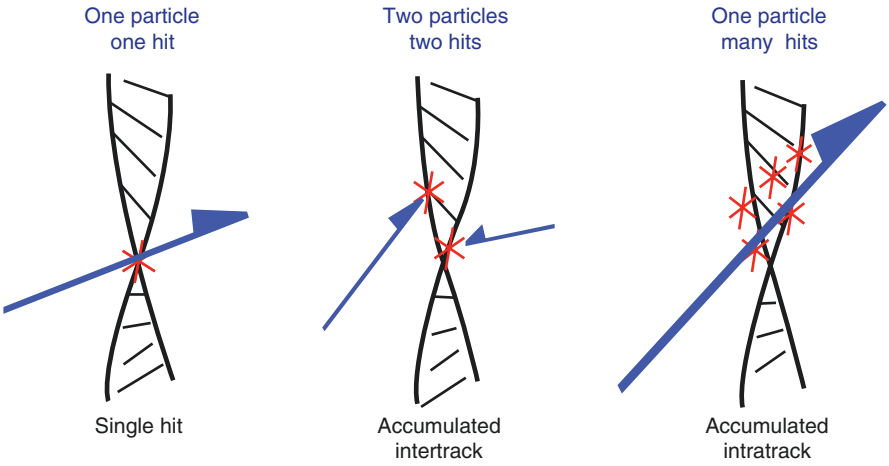

Fig. 21.2 Radiation-induced DSBs may be induced in several ways. The main difference is whether the damage is done by a single particle or by multiple particles

- **Locally multiply damaged sites** are defined as multiple DNA lesions close to one another. These are caused by multiple ionizations of water, as shown in Fig. 21.2.
  - Base damage and SSBs are easily repaired when alone, but alone, but may be very difficult to repair if clustered.
  - Two SSBs occurring close to one another are likely to become a DSB.

Single Hits and Accumulated Damage

- Conceptually, there are several ways for lethal damage (DSBs) to occur. For example (Fig. 21.2):
- **Single Hit and Accumulated Intra-track**: Damage is done by a single particle.
  - The number of DSBs formed by this mechanism is determined by total dose, but not by dose rate.
  - These lesions are more likely with **high-LET** irradiation.
- **Accumulated Inter-track**: Damage is done by two separate particles, such as two SSBs combining into a DSB.
  - The number of DSBs formed by this mechanism is determined by total dose and dose rate.
  - With low dose rate irradiation, DNA repair can prevent non-DSB damage from transforming into DSBs.

Assays for DNA Damage

- **Neutral and alkaline elution (outdated and laborious).**
  - DNA fragments are bound to a filter or column and eluted over time. Fragmented DNA is smaller and therefore elutes faster.

  - Under **neutral pH** DNA is double-stranded so you can measure **DSBs**.
  - Under **alkaline pH** DNA is single-stranded so you can measure **SSBs**.
- **Base damage.**
  - Often measured using high-pressure liquid chromatography (HPLC), usually coupled with electrochemical detection to determine specific base species.
- **Pulsed field electrophoresis.**
  - Samples of lysed cells are placed within a gel and the DNA electrophoresed to measure DNA fragmentation.

    Used for measuring DSBs.

    DSBs are indirectly determined by measuring the amount of smaller DNA fragments that enter the gel. The extent of DNA fragmentation after irradiation (compared to control cells) can be used to estimate breaks as a function of dose.
- **Comet assay (single-cell gel electrophoresis).**
  - Small numbers of single cells are embedded within a gel on a slide, and the slide is electrophoresed.

    Intact DNA is too large and cannot move; fragmented DNA migrates through the gel and forms a "tail."
  - Neutral pH conditions are used to measure DSBs but alkaline conditions can be used to measure SSBs, DSBs, and AP (abasic) sites.
  - Under special conditions the assay can be used to detect DNA–DNA and DNA–protein crosslinks.
- **γ-H2AX assay,**
  - Used as an indirect means of scoring DSBs.

    After radiation damages DNA, an amino acid residue of the histone variant H2AX is rapidly phosphorylated. This is mediated by a protein coded by the AT-mutated (ATM) gene and DNA-PKcs. The phosphorylation event results in the formation of the γ-H2AX.

    γ-H2AX formation occurs on damaged chromatin as part of a signaling cascade. DSB induction results in the formation of hundreds of γ-H2AX molecules in the chromatin flanking the DSB, such that the molecules appear to coalesce into foci ranging over megabases of chromatin. Fluorescently conjugated antibodies against γ-H2AX allow us to visualize foci at DSB sites. Number of foci per cell can therefore easily be scored.
- **Plasmid-based assays.**
  - Plasmids (circular DNA) can be made to fluoresce only if they are broken (i.e., linear instead of circular).

Chromatid and Chromosome Aberrations

- **Aberrations** are **gross mutations** created by double-strand breaks.
  - Broken DNA is sticky. If not repaired or mis-repaired, DNA fragments will stick together in the wrong order.

- **Chromosome aberrations**: An aberration occurs in an unreplicated chromosome. When the chromosome is replicated, the aberration is identical in both chromatids.
- **Chromatid aberrations**: An aberration occurs in a replicated chromosome, affecting individual chromatids.
- Some types of aberrations may be either chromosome or chromatid, while others are limited to one type.
- Aberrations may be visible upon microscopy, depending on the size of the aberration.

Stable and Unstable Aberrations

- An **unstable aberration** declines in number over time, because it is highly likely to cause cell death.
- A **stable aberration** can persist for years, because it is unlikely to cause cell death.
- **Unstable aberrations** prevent chromosomes from properly segregating during mitosis (Fig. 21.3).
- **Stable aberrations** do not affect chromosome segregation during mitosis (Fig. 21.4).

Measuring DNA Damage

- **Peripheral Blood Lymphocyte Assay.**
  - Peripheral blood lymphocytes are very sensitive to radiation, and you can count DNA aberrations in the blood:
    Conventional light microscopy generally measures unstable aberrations that disappear over days–months.
    Fluorescence in situ hybridization (FISH) can measure unstable and stable aberrations. Stable aberrations may persist for years.
- Total-body radiation doses **≥0.2 Gy** will produce measurable chromosome aberrations in lymphocytes.
  - A linear-quadratic mathematical model can be used to estimate absorbed dose from the number of aberrations (see below).
- Total-body radiation doses **>4 Gy** cannot be estimated by this technique, because the lymphocytes undergo rapid **apoptosis** and disappear.

Dose-Response: Linear-Quadratic Curve

- Plotting DNA damage versus absorbed dose results in an upward-sloping curve with a linear-quadratic shape (Fig. 21.5).
- Linear damage is directly proportional to dose and is measured by the coefficient **α**.

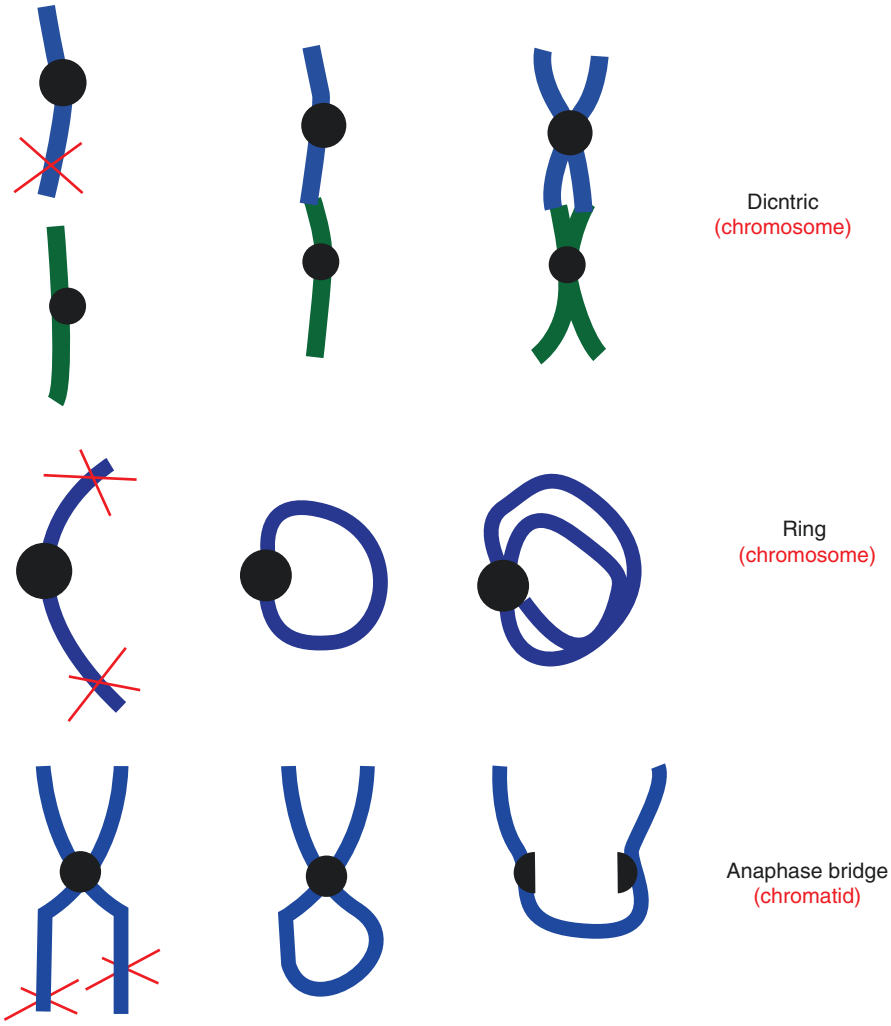

Fig. 21.3 Unstable aberrations include dicentrics, rings, and anaphase bridges

  - This represents single-hit damage and intra-track accumulated damage, which are completely independent of fraction size or dose rate.
- Quadratic damage is proportional to dose squared and is measured by the coefficient **β**.
  - This represents inter-track accumulated damage, which is strongly dependent on fraction size and dose rate.
- This curve is the rationale behind the **linear-quadratic** (**α/β**) model of cell survival.
  - See Chap. 23.

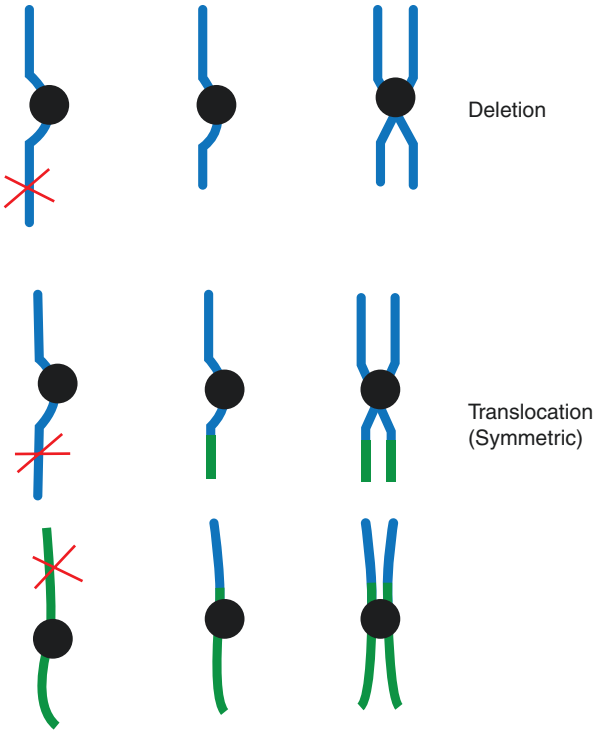

Fig. 21.4 Stable aberrations include deletions and symmetrical translocations

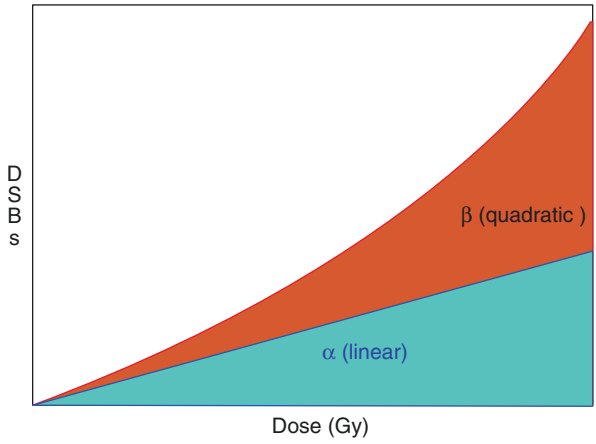

Fig. 21.5 DSB production in cells is a linear-quadratic function of dose. Total DSBs can be expressed as the sum of "linear" damage (not fraction-size-dependent) and "quadratic" (fraction-size-dependent) damage

DNA Repair (A handy list of pertinent DNA Repair Proteins and Pathways can be found in Table 21.1)

Table 21.1 A list of the more common and critical DNA repair proteins and pathways

Protein/Pathway	Function(s)
DNA glycosylases/BER	Recognizes damaged bases; some may excise DNA backbone to produce nucleotide gap
AP endonuclease (APE)/BER	Removes sugar residue and incises DNA backbone to produce SSB
DNA polymerase β, or replication factor C + proliferating cell nuclear antigen+polymerase epsilon/ BER	Synthesis of nucleotide repair patches
DNA ligase I or III/BER	Seals nick
Poly(ADP–ribose) polymerase (PARP)/SSB and DSB Repair (HR and NHEJ)	Senses nicks and activated at SSBs; synthesizes polymers of ADP-ribose; recruits or stimulates other repair enzymes, generates ATP for DNA ligation, modulates chromatin structure; facilitates HR by recruiting factors such as ATM, Mre11, and Nbs1 to sites of DSBs; In NHEJ, stimulates DNA-PK activity
ATM/DNA damage response	Phosphorylates Brca1 and Nbs1
CtIP/HR	Initiates DSB resection via promotion of endonucleolytic cleavage and processing of broken ends; its recruitment commits cells to HR pathway
Mre11/HR (and NHEJ??)	Can function as a DNA exonuclease and an endonuclease; degrades double-stranded DNA with *blunt or recessed* ends. Some evidence it may be involved in NHEJ
Rad50	Likely plays a regulatory role in the MRN complex, possibly affecting DNA or chromatin structure
Nbs1/HR	Required for redistribution of the MRN protein complex in response to DSB induction; its phosphorylation is a prerequisite for activation of the S-phase checkpoint (inhibition of DNA synthesis) upon DSB formation in normal cells
Rad51/HR	Participates in strand exchange, catalyzing the invasion of tailed duplex DNA into homologous DNA
Rad54/HR	Participates in DNA unwinding and alignment of the Rad51 protein complexes
BRCA1/HR	Promotes HR by co-localizing with γ-H2AX to the site of damage and participates in the activation of CtIP
BRCA2/HR	Appears to function in nuclear localization and loading of Rad51 onto single-stranded DNA
Resolvase/HR	Resolves Holliday junctions to separate recombining partners
DNA-PK_{cs}/NHEJ	Phosphorylates numerous NHEJ substrates; Participates with Ku in holding the two broken ends of the DNA molecule together
Ku70/Ku80 heterodimer/NHEJ	Implicated in end-joining, possibly functioning to align DNA ends or stimulating ligation
Artemis/NHEJ	Involved in processing of the break sites
XLF/NHEJ	Forms a complex with Ligase IV/XRCC4 and promotes the ligation of mismatched and noncompatible DNA ends

Table 21.1 (continued)

Protein/Pathway	Function(s)
DNA ligase IV/NHEJ	Seals the nick in the DNA
53BP1/DNA damage response	Inhibits end resection, counteracts the function of BRCA1 in HR, and promotes NHEJ
Ligase I and III/SSB Repair and A-NHEJ	Sealing of nicks resulting from SSBs; end-joining of DSBs
γ-H2AX/DNA damage response	Phosphorylated form of H2AX that forms foci at sites close to DSBs. Some evidence suggests the foci act as a beacon for accumulation of other proteins involved in the DSB repair response involved in chromatin remodeling, cell cycle checkpoints, and chromatin anchoring (to keep broken ends in close proximity)

Base Excision, Nucleotide Excision, and Mismatch Repair Pathways

- **Base excision repair (BER)** mostly removes a single damaged base during short patch repair, but synthesis of longer nucleotide patches (2-15) can also occur.
  - Can only repair very simple lesions. Bulky damage must be repaired by nucleotide excision repair (NER).
  - **Glycosylases specific for different species of base damage or APE1,** recognize base damage and remove the damaged base.
  - Removal of sugar residue mediated by APE, which leaves an apurinic or apyrimidinic site and also produces SSB.
  - **Polβ usually fills in the gap and Ligase I or III** seals the nick.
- **Nucleotide excision repair (NER)** removes the damaged base and several adjacent nucleotides.
  - This allows the repair of bulky lesions including UV photoproducts, alkyl groups, and adducts formed from cisplatin and similar agents. Not a significant player in the DNA damage response after ionizing radiation.
  - **XP family** (XPC, XPB, XPD, XPG, XPA) plus **RPA, ERCC1**, and **CSA** are responsible for repair.
  - Mutation of **XP** genes causes xeroderma pigmentosum (XP).
- **Mismatch Repair (MMR).**
  - Repairs base insertion/deletion errors that create mismatches due to replication errors and exposure to alkylating agents. Like NER, not a significant player in the radiation-induced damage response.
  - Defective MMR causes **Microsatellite Instability (MSI)**, a characteristic pattern of mutations.
  - The **MLH/MSH/PMS** gene family is responsible for mismatch repair. Mutation of these genes causes **Lynch syndrome**.

Single-Strand Break (SSB) Repair

- SSBs are formed at a high rate during/after irradiation and chemotherapy but have little effect on survival unless they combine into a DSB.
  - P**oly(ADP–ribose) polymerase-1 (PARP-1)** senses the nick and synthesizes ADP-ribose polymers. Polymerase β is usually involved in gap filling but other polymerases may be involved. DNA ligation after short-patch repair is achieved by Ligase 3 in coordination with a scaffold protein (XRCC1), and ligation after long-patch repair is completed by Ligase 1.

Double-Strand Break (DSB) Repair

- **DSB recognition and signaling**: Before a DSB can be repaired, the cell has to recognize that it has occurred, so that repair can proceed via either of two main DSB repair pathways.
  - **ATM** and **ATR** are the initial signaling molecules that detect **DSBs**.
  - ATM exists as an inactive dimer in unirradiated cells; upon irradiation and induction of DSBs, the dimer is dissociated and ATM activated.
  - Once phosphorylated, ATM can recruit and phosphorylate other proteins such as Nbs1, which is a component of the **Mre11-Rad50-Nbs1** or "**MRN Complex**." These and other proteins go on to participate in either the homologous recombination (HR) or non-homologous end-joining (NHEJ) DSB repair pathways.
  - As part of DSB signaling, **p53** and **Chk1/Chk2** are activated to cause cell cycle arrest (see Chap. 27 for more information on cell cycle checkpoint control).

    Depending on the cell type and amount of damage, this activation may lead to apoptosis.
- **Homologous recombination (HR) repair**.
  - **HR** is the predominant form of DNA repair during **late-S** and **G2**, when sister chromatids are available so as to allow a stretch of a few hundred base pairs of sequence homology to be used as a template to restore the broken DNA sequence.
  - HR is relatively **error-free**. HR usually is initiated by phosphorylation of **BRCA1** by ATM, which joins **PARP** and the MRN complex at the site of the DSB (phosphorylated Nbs1 is necessary for redistribution of MRN at the sites of DSBs). Histone H2AX is phosphorylated by ATM and becomes γ-H2AX, which then forms foci in the chromatin in the vicinity of the DSB. After DSBs are induced, **CtIP** is phosphorylated by ATM, and ubiquitinated by BRCA1, resulting in its activation and recruitment to the DNA ends, thus committing the cells to the HR pathway. CtIP and the MRN complex initiate DSB resection (Mre11 can function as an endo- and exonuclease) through endonucleolytic cleavage and processing of broken ends. After resection, the 3' DNA end invades the homologous duplex of the sister chromatid, allowing the

complementary strand of the DNA duplex to act as a template for the gap filling step. **Rad51** is key to HRR as it participates in strand exchange, facilitating the invasion of damaged DNA into the homologous DNA. **Rad54** unwinds the DNA, affording accessibility, and along with BRCA2, coordinates localization, alignment, and loading of Rad51 protein complexes. Resolution of Holliday junctions is accomplished via a resolvase.

  - Mutations in the ATM, MRE11, and NBS1 genes result in syndromes associated with enhanced radiosensitivity and predisposition to cancer (see below). BRCA1/2 mutations are responsible for hereditary breast and ovarian cancer syndromes.

- **Non-homologous End Joining (NHEJ).**
  - NHEJ occurs during G0/G1, as no sister chromatids exist. Can also occur in S and G2 phases, although HR is preferred.
  - Error-prone, since the original DNA sequence would be restorable only if two blunt ends could be religated without loss of any genetic information near the break sites; may lead to mutation or cell death.
  - DSB induction results in recruitment of the **Ku70/Ku80 heterodimer** to the DSB site to bind the free ends. Recruitment of the **catalytic subunit of DNA-dependent protein kinase (DNA-PK$_{cs}$)** follows, with Artemis also joining the mix. Phosphorylation and activation of **Artemis** by DNA-PK occur, allowing Artemis to function as an exonuclease in processing the lesion. Gaps are filled by a DNA polymerase. Protein–protein interactions between DNA-PKcs molecules bridge the site at the DNA ends. Processing and gap-filling promote stimulation of the ligation reaction by **XLF**. DNA-PK recruits **DNA Ligase IV** and its associated factor, **XRCC4**, and these proteins facilitate the ligation of ends (which may be mismatched or noncompatible after processing). DNA-PK$_{cs}$ is also known to phosphorylate the histone H2AX to γH2AX in the chromatin in the vicinity of a DSB.

    An **alternative deletional (A-NHEJ) pathway** exists, which requires microhomology to join ends of DSBs with small deletions. The A-NHEJ pathway is Ku-independent, but requires **DNA ligase III and PARP I**.

- DSBs are the main mechanism of radiation-induced cell killing, so any defect in DSB repair can increase radiation sensitivity (Fig. 21.6).

Human Genetic Diseases Due to Deficient DNA Repair

(many are also associated with a predisposition to cancer)

- **NER disorders (genes in parentheses).**
  - **Xeroderma pigmentosum (XP-gene family).**
    Photosensitive and very high skin cancer risk.
    UV hyper-sensitive, not radiosensitive.
  - **Cockayne Syndrome (CSA/CSB).**
    Photosensitive but no cancer risk.

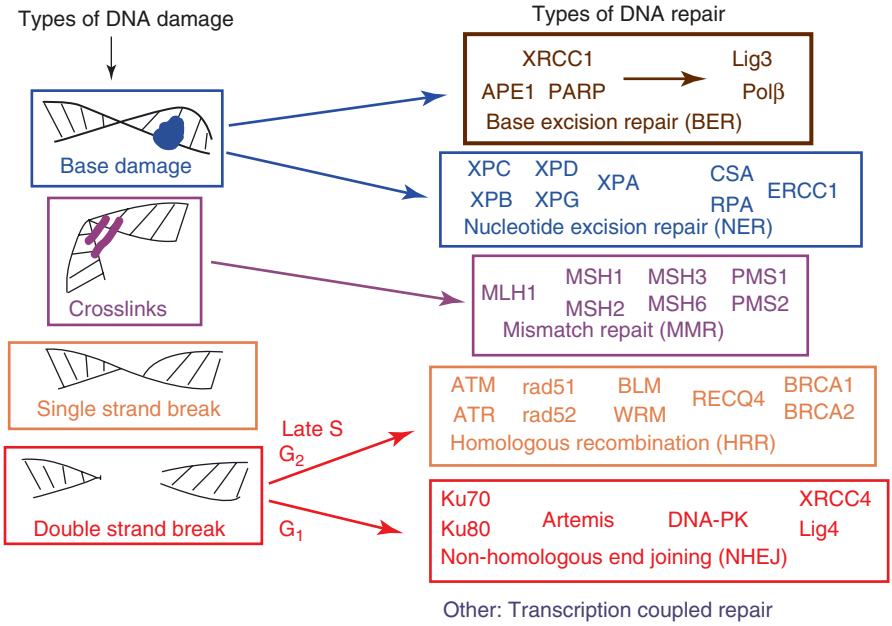

Fig. 21.6 DNA damage may be repaired by one of many different pathways, depending on the type of the damage and the phase of the cell cycle

UV hyper-sensitive, not radiosensitive.

- **MMR disorders.**
  - **Lynch syndrome (MLH/MSH gene family).**
    Extremely high risk of colorectal cancer.
    Not radiosensitive but may be hyper-sensitive to chemotherapy.
- **HR disorders.**
  - **Hereditary Breast and Ovarian Cancer Syndrome (BRCA1/BRCA2).**
    Self-explanatory syndrome name.
    Despite the DNA repair defect, BRCA1/2 patients are not extremely radiosensitive.
- **Disorders affecting multiple repair pathways.**
  - **Ataxia Telangiectasia (ATM).**
    Multiple neurologic and immunologic symptoms, plus high risk of multiple cancers.
    Extremely radiosensitive.
  - **Ataxia-Telangiectasia Like Disorder (Mre11).**
    Clinically similar to ataxia-telangiectasia.
    Extremely radiosensitive.
  - **Nijmegan Breakage Syndrome (Nbs1).**
    Extremely radiosensitive.
  - **Li-Fraumeni Syndrome (p53).**

Numerous cancers at a young age.
Somewhat radiosensitive, and very high rate of radiation-induced malignancies.

- **Other disorders associated with radiosensitivity.**
  - Basal cell nevoid syndrome, Cockayne syndrome, Fanconi anemia, Gardner syndrome, Usher syndrome, Warner syndrome, Bloom syndrome, Down syndrome.

Exploiting DNA Repair Defects During Therapy: Concept of Synthetic Lethality

- Synthetic lethality is a term used if the combined deficiencies in the functioning or expression of two or more gene products lead to cell death, but a deficiency in only one of these genes or its corresponding gene products would not result in cell death.
- A good example of synthetic lethality involves the use of PARP inhibitors (see Chap. 31 for more information on PARP inhibitors). PARP is a critical enzyme involved in SSB repair but is not critical for DSB repair. However, the BRCA1 protein is critical for repairing DSBs. If we inhibit PARP1, this action would be selectively lethal to BRCA1-deficient cancers (e.g., tumors with BRCA mutations), since the tumor cells would tend to accumulate of SSBs that would eventually get converted to DSBs during DNA replication and which WOULD NOT be repairable due to a deficiency in BRCA mutants.

Modes of Cell Death and Survival Assays

22

Introduction

There are many ways that normal and tumor cells can die from radiation injury. Extensive DNA damage may result in mitotic catastrophe or senescence, or necrosis with corresponding inflammation. Alternatively, some cell types may undergo apoptosis, an orderly "programmed" dismantling of the cell that does not involve the inflammatory process. However, other modes of death, such as necroptosis and autophagy (and even submodes) have been identified, with their relevance to the overall radiation response being an active area of investigation. It should be noted that there is no general response to radiation by all cells, since mode of death may be dose- and cell-type dependent. Cell survival under various conditions can be measured using in vitro and in vivo assays. Different assays are suitable for measuring different endpoints in tumors and normal tissues. However, clonogenic cell survival is generally regarded as the gold standard for measuring loss of reproductive integrity after irradiation, regardless of the mode of death.

Definition of Cell Death

- In radiobiology and especially in the clinic, we are usually most interested in **reproductive cell death**.
  - Death is defined as **loss of reproductive ("clonogenic," "colony forming") capability**.
- This definition is very relevant when considering eradication of tumors and inhibition of growth. If tumor cells cannot reproduce, they are no longer clonogenically viable.
- Loss of reproductive integrity is also relevant to rapidly dividing normal tissues (e.g., gut or bone marrow).
- This is not so relevant to highly differentiated normal tissues that normally do not divide (nerves and muscles are already "dead" by this definition).

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- Cells with extensive DNA damage may divide for a few times before becoming unable to divide further.
  - At this point, the cell is reproductively dead, or **nonclonogenic**. It is incapable of producing a colony in vitro or re-establishing a clone or tumor in vivo.

Modes of Cell Death After Irradiation

- **Necrosis**
  - A "passive" form of cell death.
    Random fragmentation of DNA.
  - DNA fragments produce "smears" on an agarose gel.
    Cell swells and usually ultimately the cell membrane bursts.
    Other cell organelles swell.
    A proinflammatory process.
  - May be induced by trauma, hyperthermia, hypothermia, hypoxia, oxidative stress, chemotherapeutic agents, and so on.
- **Apoptosis**
  - The most common form of **programmed cell death**.
  - Also known as **interphase death**, to differentiate it from mitotic death.
  - Cell undergoes a series of orderly and degenerative changes.
    Controlled digestion of proteins (via caspases) and DNA (via a calcium/magnesium-dependent caspase-activated DNase [CAD] endonuclease).
    DNA "laddering" can be observed in agarose gels, representing cleavage of DNA into oligonucleosomal fragments that are multiples of 180–200 base pairs.
    Plasma membrane stays intact, so apoptotic cells will not stain with vital dyes.
    Plasma membrane blebbing results in the formation of "apoptotic bodies" (in which intact organelles may be found); this blebbing results in shrinkage of the cell.
    No inflammatory response.
    Energy-dependent; usually requires transcription and translation.
    Translocation of the phospholipid phosphotidylserine to other leaflet of plasma membrane.
    May be triggered by caspases acting via two signaling pathways: intrinsic and extrinsic.
  - An important part of normal embryonic development.
    The disappearance of the interdigital webbing in the hands of some mammals and regression of tadpole tails are examples of apoptosis.
  - Apoptosis occurs in response to radiation in some but not all cells.
    Very radiosensitive cells like normal lymphocytes, lymphoma, and neuroblastoma cells have a lot of apoptosis.
    Very radioresistant tumor cells like melanoma and glioblastoma have no meaningful apoptosis.
    Like necrosis, may be induced by trauma, hyperthermia, hypothermia, hypoxia, oxidative stress, chemotherapeutic agents, and so on.

Autophagy

- Cell degrades its own components using lysosomes.
- Typically occurs in response to nutrient deprivation; however, many human cancers including pancreatic adenocarcinomas depend on autophagic recycling of cellular components to support tumor cell growth.
- Often a normal part of cell growth/development and allows cells to strike a balance between synthesis, breakdown, and reutilization of cellular components, notably in response to cell starvation.
- The degradation of cellular components by the lysosome is triggered by proteins coded by autophagy-related, or ATG, genes notably Atg8 and Atg6 (or LC3 and Beclin-1, respectively, in mammalian cells).
- Involves formation of the autophagosome, which sequesters an organelle or material and then fuses with a lysosome, where degradation of autophagosome contents occurs.
- May be induced via inhibition of mTOR, activation of PI3K, mitochondrial activation of ERK, or activation of JNK.
- Chloroquine and Hydroxychloroquine which have been used as treatment and prophylaxis for malaria have been shown to inhibit autophagy in human cancers.
- **Mitotic Catastrophe** (aka mitotic death)
  - This occurs when cells are unable to properly segregate their chromosomes during mitosis. Cell death occurs from massive DNA damage. Cells often cannot complete cytokinesis and usually become "giant" multinucleated cells that contain several micronuclei.
  - Mitotic catastrophe is caused by lethal DNA aberrations, which are caused by DSBs from irradiation.
    Refer to Chap. 21 for more details.
  - The DNA aberration is not lethal until the cell attempts mitosis, so there is a time delay between irradiation and mitotic catastrophe.
    Depending on the type, this is why it takes days to weeks for a tumor to regress after irradiation.
- **Senescence** (cessation of cell cycle)
  - Cells remain intact but become unable to divide due to DNA damage. This makes them "reproductively dead" even though the cells are still there.
  - Senescence is a normal part of cellular aging but may also happen in response to injury, including radiation.
  - p16 and β-galactosidase are molecular markers of senescence.
- **Necroptosis**
  - Another regulated form of cell death.
  - Caspase-independent.
  - Cell death is executed by "receptor-interacting protein kinases" RIP1 and RIP3, MLKL.
  - **F**ormation of the necrosome (a complex of RIP1, RIP3, and MLKL) mediates downstream events like a reactive oxygen species (ROS) burst, plasma membrane permeabilization.

  - RIP1 must phosphorylate and activate RIP3, and RIP3 must phosphorylate MLKL to form the trimer.
  - The MLKL trimer translocates to the plasma membrane, causing plasma membrane permeabilization. This is a key execution mechanism. N**ecroptosis can be inhibited** by agents that act on RIP1, RIP3, and MLKL.
- **Alternative forms of programmed cell death**
  - **Anoikis**: Programmed cell death that occurs when cells are placed in an unfamiliar organ or tissue. Cancer cells must overcome anoikis to metastasize. The BIM-EL protein is associated with this process. It facilitates cytochrome C release from mitochondria, in turn activating caspases and triggering DNA fragmentation similar to what is observed during apoptosis.

Tissue Effects After Irradiation: When Do the Characteristics of the Major Modes of Death Become Evident?

- **Apoptosis** usually begins within **6–24 h** after irradiation; however, delayed apoptosis (several days) has also been observed, and initial apoptotic changes may be noted earlier in some cell lines depending on stimuli and dose.
  - Apoptotic bodies are rapidly degraded by bystander cells, so they quickly disappear.
- **Mitotic catastrophe** usually happens within one to two cell cycles (**15 h to 2 weeks** in actively cycling cells).
- **Necrosis** may be observed for days to a small number of weeks after irradiation. At very high doses, it may occur within minutes to hours of irradiation.
- **Late responses**: Irradiated tissues may show changes **months to years** after radiation.
  - These changes may not be directly linked to cell killing.
  - Fibrosis, microvascular changes, chronic inflammation, decreased wound healing.

Molecular Pathways of Apoptosis

- Apoptosis requires an orderly sequence of events to destroy the cell without causing any inflammation.
- There are two major pathways by which apoptosis is initiated: intrinsic and extrinsic.
- **Intrinsic pathway of apoptosis** is initiated by cellular stress or DNA damage.
  - **ATM senses DNA damage and signals p53** which activates proapoptotic **Bax/Bak/Bad**. This leads to pore formation in the mitochondrial membranes.
  - Once the mitochondria become sufficiently porous, **cytochrome c** leaks out and activates **Caspase 9**, the intrinsic pathway **initiator caspase** that goes on to activate killer caspases such as 3 and 6.

  - This can be part of the radiation response in some normal cells such as lymphocytes or in cancers such as lymphoma.
  - Antiapoptotic **Bcl-2** and **Bcl-XL** suppress mitochondrial pore formation and are therefore pro-survival.
- **Extrinsic pathway of apoptosis** is initiated by the **Fas** or **TNFR** receptor.
  - These bind death-promoting ligands **FasL** and **TNF**, respectively.
  - This leads to cleavage and activation of **caspase 8**, the extrinsic pathway **initiator caspase**.
  - Tumors can express death ligands in order to cause apoptosis in T cells, suppressing the immune response (Fig. 22.1).
- Once **caspase 8 or 9** (initiator caspases) is activated, it rapidly activates **caspases 1, 3, 4, 6, 7** (effector caspases).
  - The effector caspases form an irreversible protease cascade, with each protease activating more proteases to cause cell death.
  - The cell membrane remains intact, so cell contents do not leak out into the interstitial space. Instead, cell contents are neatly packaged into apoptotic bodies for digestion by neighboring cells.
- Cancer cells are often deficient in apoptosis. This may happen in one of two ways:

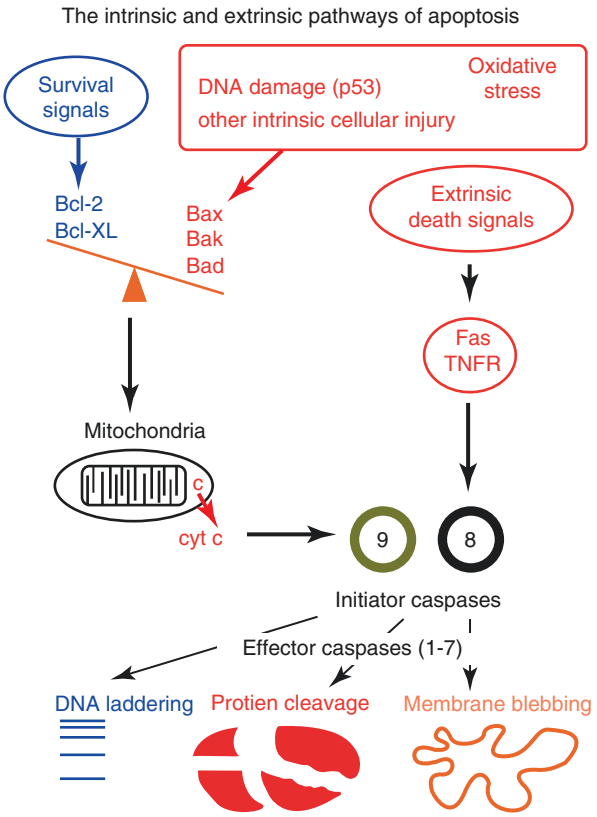


Fig. 22.1 The intrinsic and extrinsic signaling pathways of apoptosis. Apoptosis is initiated by caspase 8 (extrinsic) and caspase 9 (intrinsic), which can be remembered as billiard balls! If the cell is behind the 8-ball, it is dead

  - **Increased antiapoptotic signal**: For example, **EBV** makes a viral homolog of **Bcl-2**. This predisposes to lymphomas and nasopharyngeal cancers.
  - **Decreased proapoptotic signal**: For example, **HPV** makes **E6** and **E7** which suppress **p53** activity. This predisposes to squamous cell cancers.

Survival of Viruses, Bacteria, and Eukaryotic Cells After Irradiation

- Radiosensitivity depends on three main things: DNA content (or "target" size), repair mechanisms, and mode of death.
  - More DNA = easier target to hit = more sensitive.
  - More repair = less sensitive.
  - More apoptosis = more sensitive.
- **Mammalian cells** are highly radiosensitive because they have lots of DNA and can undergo apoptosis.
  - **~2 Gy** can kill approximately half of mammalian cells, **~70 Gy** delivered in 2 Gy fractions can sterilize a tumor.
- Yeast and bacteria are far more resistant, due to much lower DNA content (smaller target size).
  - **~10s to 100s of Gy** will kill half of bacteria and yeast.
  - A food-processing irradiator may deliver up to 20,000 Gy to sterilize bacteria.
- **Viruses** are extremely radioresistant because they have so very little DNA (and thus have a smaller target size) compared to a eukaryotic cell. Certain bacteria such as *Micrococcus (Deinococcus) radiodurans* are radioresistant due to DNA repair.
  - Lethal dose in the kiloGray range.

Mammalian Cells: Effects of Fraction Size, Dose Rate, and Cell Type

- Cell survival *usually* decreases as fraction size and dose rate increase. This is due to decreased opportunity for cells to repair DNA damage.
  - For a detailed discussion, see Chap. 23.
- Nondividing cells are the most radioresistant while rapidly dividing cells with active apoptosis are highly radiosensitive.
  - For a detailed discussion, see Chap. 25.

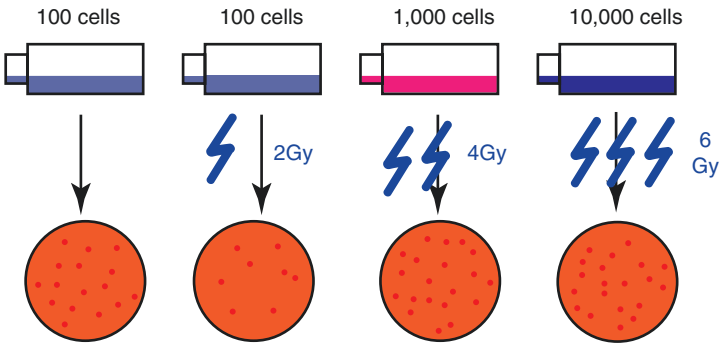
A Word on Assays

- **In vitro assays** measure the survival of cell lines under nonphysiological conditions.
  - This allows for very careful control of all variables:
    Oxygen, temperature, nutrient levels.
    Precise drug concentrations.

  - In vitro assays are nonphysiological:
    Single cell type with no vasculature.
    No normal tissue or immune cells present.
    Cannot measure late effects.
- **In vivo assays** measure cell survival, normal tissue function, or tumor growth in an experimental animal.
  - Advantages of in vivo assays include the following:
    Tissues and vasculature are intact.
    Tumor can interact with surrounding normal tissues.
    Can measure early as well as late effects if you wait long enough.
  - Biological response will occur under more physiological conditions in an organ or tissue rather than in culture dishes.
  - Animal experiments are still very different from human patients:
    Animal cells have different tolerances for radiation and chemotherapy.
    Many experimental animals are not immunocompetent so there are no immune effects.

In Vitro Clonogenic Survival Assay

- **Clonogenic survival** is defined by the ability to form colonies. Therefore, survival is measured by plating out cells and seeing how many colonies they form (Fig. 22.2).
- Even in the absence of radiation, not every cell put on a plate will form a colony.
  - **Plating Efficiency (PE)** = % colony formation with no dose.



Colonies	80 %	40 %	10 %	1 %
SF =	100 %	50%	12.5 %	1.25 %

Fig. 22.2 The clonogenic survival assay. Surviving fraction may be calculated by dividing the percent colonies formed by the plating efficiency (percent colonies formed without irradiation)

- Therefore, the % colonies formed at any given dose level must be divided by the % colonies at zero dose to get the **surviving fraction (SF)**.

$$\mathrm{SF}\left(\mathrm{Dose}\right)=\frac{\%\mathrm{colonies}\ \left(\mathrm{Dose}\right)}{\%\mathrm{colonies}\ \left(\mathrm{No\ dose}\right)} \tag{22.1}$$

In Vivo Normal Tissue Assays

- **Jejunal crypt stem cell assay** (Fig. 22.3)
  - Early responding tissue.
  - Mouse intestines are irradiated with enough dose (≥11 Gy) to destroy the villi.
  - After **3.5 days**, some of the jejunal crypts will start to regenerate.
    1 regenerating crypt = 1 surviving clonogenic cell.
    Endpoint = crypts per circumference.
- **Bone marrow stem cell assay (Till and McCulloch)**
  - Early responding tissue.
  - **Donor mice** irradiated with a test dose.

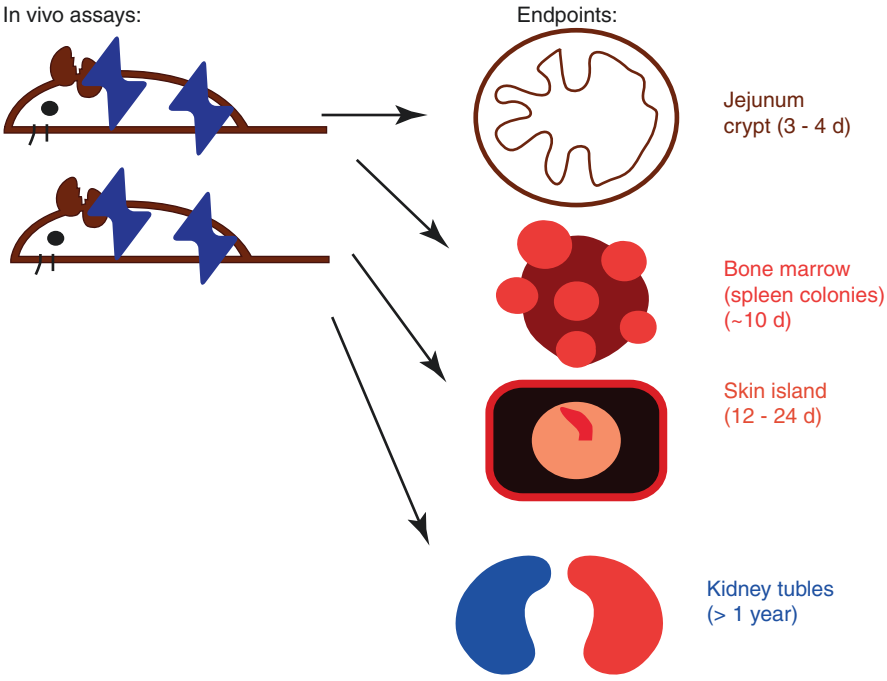


Fig. 22.3 Animal normal tissue assays. The time it takes following irradiation to observe each endpoint depends on whether it is an early or late responding tissue

  - **Recipient mice** irradiated with a supralethal dose ≥9 Gy (all bone marrow cells are killed).
  - **Donor bone marrow** injected into **recipient mice**.
  - Donor stem cells form **colonies** in the spleen which can be easily counted (this takes ~**10 days**).
    1 colony = 1 surviving clonogenic cell.
    Endpoint = colonies per 10^n donor stem cells.
- **Skin clone assay**
  - Early responding tissue.
  - High dose radiation used to create a "moat" of dead skin, with an "island" of intact skin in the middle.
  - The skin "island" is then irradiated with a test dose.
  - This area of skin regrows after **12–24 days** as a series of nodules.
    1 nodule = 1 surviving clonogenic cell.
    Endpoint = skin nodules per cm^2.
- **Kidney tubule assay**
  - Kidney is a late responding tissue.
  - For each mouse, one kidney is irradiated and one is spared.
  - **Wait 60 weeks**, and then compare number of intact kidney tubules on irradiated side versus unirradiated side.
    Endpoint = % of tubules intact.

Experimental Tumor Models

- **Spheroid systems** (Fig. 22.4)
  - Must use a tumor cell line that grows as **spheroids** in cell culture (clumps of many cells, not single cells).
    Spheroids are more "in vivo like" than a monolayer of cells, but less complex than what is found in an animal tumor model.
  - Spheroids are irradiated while intact, and separated into single cells for plating and colony formation.
- **Tumor growth measurements**
  - Control animals have untreated tumors.
  - Experimental animals receive radiation to their tumors.
  - Primary endpoint = **growth delay**.

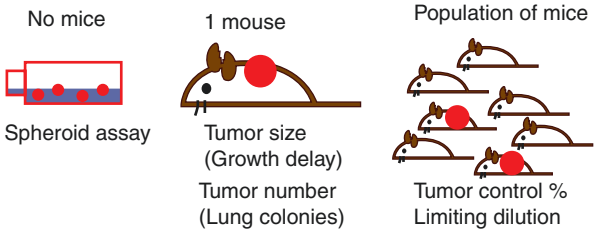


Fig. 22.4 Experimental tumor models. Tumors differ from single cells because they are macroscopic in size, so the center of a tumor has less access to oxygen and nutrients than the core

– (Days for tumor to grow to X size after treatment) − (Days for untreated tumor to grow to X size).

- **Tumor lung colony assay**
  - Must use a mouse tumor with very high tendency to form lung metastases (i.e., mouse sarcoma).
  - Inject tumor cells into recipient mouse, wait for lung colonies to form, and count them.
  - Count **lung colonies** in mice injected with irradiated and unirradiated tumor cells:

$$\mathrm{SF}\left(\mathrm{Dose}\right)=\frac{\mathrm{Colonies}\ \left(\mathrm{Dose}\right)}{\mathrm{Colonies}\ \left(\mathrm{No\ dose}\right)} \tag{22.2}$$

- **TCD_{50} tumor control assay**
  - Groups of animals with the same tumor are treated with different doses of radiation.
  - Primary endpoint = **Tumor Control Dose 50 (TCD_{50})**.
    - Dose required to control 50% of tumors
  - Very reproducible number for established tumor cell lines in inbred animals.
  - Used to compare tumor control doses with single-fraction and fractionated radiation.
- **Tumor limiting dilution assay**
  - **Transplantable leukemia** in **mice** can be transmitted by intraperitoneal injection.
  - Primary endpoint = **Tumor Dilution 50 (TD_{50}).**
    Number of leukemia cells required to induce a leukemia in 50% of recipient mice
  - Compare leukemia cells from irradiated and unirradiated leukemic mice:

$$\mathrm{SF}\left(\mathrm{Dose}\right)=\frac{\mathrm{TD}_{50}\ \left(\mathrm{No\ dose}\right)}{\mathrm{TD}_{50}\ \left(\mathrm{Dose}\right)} \tag{22.3}$$

- **In vivo/in vitro assay for measuring clonogenic cell survival**
  - Must use a tumor cell line that is capable of growing both **in vivo** (in a mouse) and **in vitro** (in a culture dish).
  - Tumors are grown and treated in mice.
    Tumors are then excised, cells plated out, and colonies are counted like in an in vitro cell culture assay.
  - This allows for an in vitro measurement of cell survival after irradiation in vivo.

Assays or Methods for Distinguishing Modes of Death

- Apoptosis: Agarose gel electrophoresis (to detect nonrandom DNA fragmentation, e.g., DNA "laddering"); TUNEL assay (detects DNA fragmentation by fluorescent labeling of broken ends); Annexin V/Propidium iodide staining (flow or image cytometry can be used to detect cells that stain for Annexin V but exclude propidium iodide); Caspase activation or cleavage of specific proteins; Morphological analysis (blebbing, chromatin condensation).
- Necrosis: Agarose gel electrophoresis (to detect random DNA fragmentation, e.g., a smear); Morphological analysis (cell swelling and bursting).
- Autophagy: Detection of localization of autophagic ATG proteins to pre-autophagosome or autophagosome structures;
- Mitotic catastrophe/senescence: Morphological analysis (multinucleation, giant cell); Measurement of expression of β-galactosidase.
- Necroptosis: Formation of the RIP1–RIP3–MLKL trimer.
- Anoikis: Detection of increased BIM-EL activity and mitochondrial cytochrome *c* release.

Radiation Survival Models, SLD, PLD, and Dose Rate

23

Introduction

Post-irradiation cell survival as a function of radiation dose can be biophysically modeled in several different ways, using Poisson statistics as the basis for survival equations. The single-hit, multitarget model has parameters D_0, the dose correlating with one hit per cell, and D_q, which is the width of the "shoulder," and correlates with repair capacity. The linear-quadratic (LQ) model utilizes terms α (single-hit kill) and β (two-hit kill) which correlate with low-dose killing and high-dose killing, respectively. The LQ model can be used to determine biologically equivalent doses between various dose fractionation schemes. The various survival curve parameters can be altered if irradiated cells undergo either sublethal damage repair (which is modeled with split dose experiments), potentially lethal damage repair (which is modeled with plating delay experiments), or if cells are irradiated at low or ultra-high dose rates. In addition to these two commonly used models, there are multiple other models that have their own strengths and weaknesses.

A Note on Mathematical Modeling

- This chapter focuses on survival models for irradiation: single-hit multitarget, two-component, linear-quadratic, and models of biologically effective or equivalent dose.
- All of these mathematical models are different ways to interpret the available data (cell survival, tumor control).
  - The **linear-quadratic (α/β) model** is most commonly used in the clinic due to its simplicity.
  - Far more sophisticated models exist in the literature.

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Poisson Statistics: What Are They?

- **Poisson statistics** describe a *large number* of random events happening to a *large number* of subjects, averaging out to a *small number* of events per subject (Fig. 23.1).
  - This is a pretty good approximation of radiation hitting cells.
  - At an average of **X events per subject**:
    (e^{-X}) subjects have no events.
    ($1 - e^{-X}$) subjects have at least one event.

Poisson Statistics and Cell Survival

- The Poisson model is used for *surviving fraction* (**SF**) of cells:
  - At an average of **X lethal hits per cell**:
    (e^{-X}) cells survive (no hits).
    ($1 - e^{-X}$) cells die (at least 1 hit).
  - Based on this equation,
    @ 1 hit per cell: SF = 0.37 (i.e., D_{37} or D_0)
    @ 2 hits per cell: SF = 0.14
    @ 2.3 hits per cell: SF = 0.10
    @ 3 hits per cell: SF = 0.05

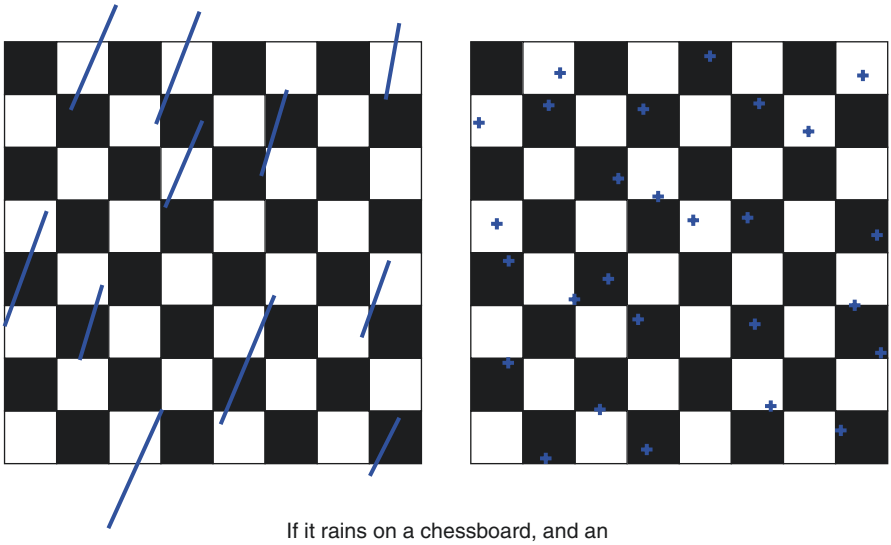

Fig. 23.1 Poisson statistics. This class of statistics may be described by the "raindrop analogy" as shown above. This is relevant to radiotherapy as radiation hitting cells is rather similar to raindrops hitting a board

  - **D_0** is defined as *the radiation dose resulting in 37% survival*. This is assumed to be equal to the radiation dose necessary to cause one lethal hit per cell.
- Poisson is also used for *tumor control probability* (**TCP**):
  - At an average of **X surviving tumor cells per patient**:
    (e^{-X}) patients are cured (no tumor cells).
    ($1 - e^{-X}$) patients recur (at least 1 tumor cell).
  - Based on this equation,
    @ 1 tumor cell per pt.: **TCP = 0.37**
    @ 0.5 tumor cells per pt.: **TCP = 0.61**
    @ 0.1 tumor cells per pt.: **TCP = 0.90**
    @ 0.05 tumor cells per pt.: **TCP = 0.95**
    @ 0.01 tumor cells per pt.: **TCP = 0.99**
  - **Rule of Thumb**: To achieve a certain **TCP**, you should aim for a tumor cell survival of (**1 − TCP**).

Single-Target, Single-Hit Model

- This model assumes that each cell has one target which if hit will result in death of the cell.
- For a single dose D:

$$\mathrm{SF}(\mathrm{D}) = e^{-\mathrm{D}/\mathrm{D0}} \tag{23.1}$$

  - **D_0** ("D-Zero") = dose required to cause 1 lethal hit per cell.
  - **n** = 1.
  - **D_q = 0.**
  - When you plot your **SF** data points versus **Dose** on a semilog chart, it would be a straight line, indicating survival is an exponential function of dose. That is, a straight line on a semilog graph means pure exponential killing which is defined only by D_0. If $D = D_0$, $SF = e^{-D_0/D_0} = e^{-1} = 1/e = 0.37$ which is also called D_{37}.
  - This type of survival curve is seen for mammalian cells which are irradiated with high LET (densely ionizing) radiation such as alpha particles or carbon ions (see Chap. 24); very radiation-sensitive cells like lymphocytes and bone marrow cells (see Chap. 25); cells that have major defects in DNA double-strand break repair (Chap. 21); are synchronized in M phase; and for cells that have DNA double-strand break repair inhibited by chemical or gene knockdown.

Multitarget, Single-Hit Model

- This model assumes that each cell has multiple independent targets, all of which must be hit to kill the cell.

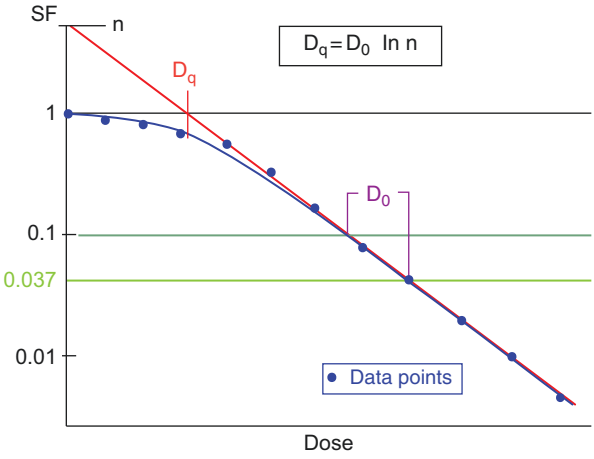

Fig. 23.2 The single-hit, multitarget survival curve. Notice that it is curved at low doses and straight (e.g., survival is an exponential function of dose) at high doses. This allows you to calculate D_0 by taking measurements in the high-dose region

- For a single dose D,

$$SF(D) = 1 - \left(1 - e^{-\frac{D}{D_0}}\right)^n \tag{23.2}$$

  - **D_0** ("D Zero") = dose required to cause 1 hit per cell.
  - **n** = extrapolation number.
  - **$D_q = D_0 * \ln n$** = quasi-threshold dose.
- This looks complicated, but it is much easier to understand if you draw a picture, as shown in Fig. 23.2.

Single-Hit, Multitarget Model: Drawing a Survival Curve

- Plot your **SF** data points on a semilog chart.
  - **ln SF** = logarithmic y-axis.
  - **Dose** = x-axis.
- Draw a straight line that connects all of the high dose points (Fig. 23.2).
  - **Y-axis intercept = ln n.**
  - **X-axis intercept = D_q.**
  - **Slope = $D_0 = D_q/\ln n$.**

Single-Hit, Multitarget Model: D_0 and D_Q

- The high-dose portion of the curve is actually a straight line:
  - **D_0** is defined as the additional dose required to reduce surviving fraction to 37% of what it was before.

Do not measure D_0 at SF = 0.37 if the survival curve has a shoulder. Remember that D_0 applies to the high-dose portion of the curve in that case! Instead, measure the difference in dose between SF = 0.1 and SF = 0.037.

  - **D_0** is a measure of the cell's inherent radiation sensitivity. Most **D_0** values are somewhere around 1 Gy.
  - **$D_{10} = 2.3 \times D_0$** = a dose that will reduce surviving fraction by tenfold (i.e., from SF = 0.1 to SF = 0.01).
- The low-dose portion of the curve is known as the "shoulder":
  - **D_q** tells you how wide the shoulder is.
  - **D_q** is a measure of the cell's repair capacity. More repair means a larger D_q and a larger shoulder.
  - This type of survival curve is very common for many mammalian cells with intact DNA repair with intermediate and higher resistance to radiation-induced low LET X-ray and gamma ray killing.

Single-Hit, Multitarget Model: Advantages and Disadvantages

- **Advantages**:
  - The high-dose portion of the curve is a straight line. You can draw a single-hit curve with a pencil and a ruler. This makes it the simplest of the cell survival models and useful for "paper napkin" calculations.
  - This straight-line component correlates well with cell-culture experiments. The single-hit model is more accurate at high doses than at low doses.
- **Disadvantages**:
  - The low-dose portion of the curve greatly underestimates cell kill.
  - Unlike the linear-quadratic model, the single-hit model is not based on a molecular mechanism.
  - Unlike the linear-quadratic model, there is not a simple equation for "equivalent dose" given a daily fractionation schedule.

Fractionated Radiation and Effective D_0

- A fractionated radiation survival curve has a shallower slope compared to a single-fraction survival curve.
  - Assuming complete repair in between fractions, the shoulder is repeated with each fraction (Fig. 23.3).
- The slope of a fractionated survival curve is called **effective D_0**.
- For a single fraction of **D** Gy with a surviving fraction of **SF_D**:

$$\text{Effective}\,D_0 = -\ln\left(SF_D\right)/D \tag{23.3}$$

$$\text{Effective}\,D_{10} = -\log\left(SF_D\right)/D = 2.3 \times \text{Effective}\ D_0 \tag{23.4}$$

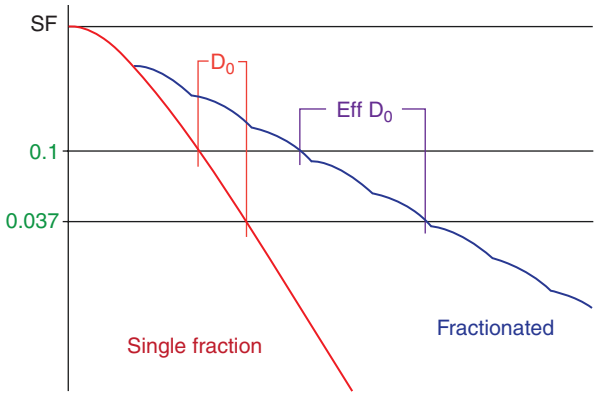

Fig. 23.3 D_0 versus effective D_0. When radiation is fractionated, you need much more dose to achieve the same amount of cell kill. Therefore, effective D_0 is always larger than D_0

- After **X** fractions to total dose **XD** Gy:

$$SF_{XD} = SF_D^X = e^{-\frac{XD}{\text{Effective } D_0}} \tag{23.5}$$

- **Effective D_0** is always larger than true **D_0**.
  - At $SF_{2\,Gy} = 0.5$, **Effective D_0 = 2.89 Gy**.
  - Compare this to a typical **D_0** of ~**1.1 Gy**.

Fractionated Radiation: Solving Survival Questions

- First figure out the answer for a question that is asking for a **surviving fraction (SF)** or a **tumor control probability (TCP), consider the following:**
  - **(1)** "What is the dose needed to kill 99% of tumor cells?"
    This is asking for an **SF = 0.01**.
  - **(2)** "What is the dose needed to give 99% tumor control of a tumor with 10^9 cells?"
    This is asking for a **TCP = 0.99**, which equals **0.01** tumor cells.
    SF = $0.01/10^9 = 10^{-11}$.
- Then figure out an **effective D_0** (=**ln(SF)/D**).
- **Effective D_{10} = 2.3 * Effective D_0.**
- Each effective D_{10} will reduce SF by tenfold:
  - To achieve an SF = 0.01, total dose = 2 * eff D_{10}.
  - To achieve an SF = 10^{-11}, total dose = 11 * eff D_{10}.

Linear-Quadratic (LQ, Alpha-Beta) Model

- The **linear-quadratic model** was developed after the in vitro observation that DNA damage follows a linear-quadratic relationship with dose **D** (Fig. 23.4).
- **Lethal DNA aberrations = αD + βD² = Cell Kill**

$$SF_D = e^{-(\alpha D + \beta D^2)} \tag{23.6}$$

- Unlike the single-hit model, the **LQ model** accounts for two different types of lethal hits which are based on known molecular mechanisms of DNA damage:
  - **Single-hit kill** (**α**) is unrepairable damage and is independent of fractionation or dose rate.
    This corresponds to single-hit and intra-track accumulated damage (see Chap. 19).
  - **Two-hit kill** (**β**) is repairable damage and depends on fractionation and dose rate.
    This corresponds to inter-track accumulated damage (see Chap 21).
- The **α/β ratio** is the dose at which **α** kill and **β** kill are equal.
  - **Low α/β ratio** ("high repair") tissues are relatively resistant at small fraction size and relatively sensitive at large fraction size.
  - **High α/β ratio** ("low repair") tissues are relatively sensitive at small fraction size and relatively resistant at large fraction size.
- **NB:** All the survival curve biophysical parameters described above (D_0, n, D_Q, α, and β) for various mammalian cells can be modified, that is, increased or decreased by the 4/5Rs of radiobiology described below.

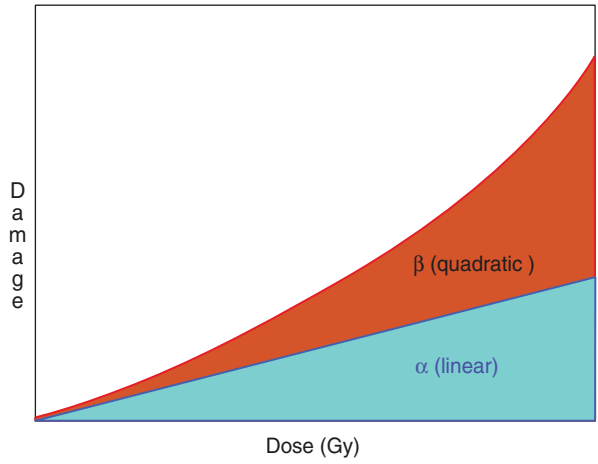

Fig. 23.4 The linear-quadratic DNA damage curve. Total DNA damage can be expressed as the sum of "linear" damage (not fraction size-dependent) and "quadratic" (fraction size-dependent) damage. The figure is repeated from Chap. 21

The "4 Rs" of Radiobiology

- Fractionated RT is biologically superior to single-fraction RT in most situations, and the "**Four Rs**" play a role in the biological effects of fractionation:
  - **R**epair (sublethal and potentially lethal damage repair)
  - **R**eoxygenation (acute and chronic hypoxia)
  - **R**edistribution (cell cycle and dose rate effects)
  - **R**epopulation
- **Repair** is discussed in this chapter.
  - Repair increases cell *survival* after fractionated radiation, both for tumors and normal tissues.
- **Oxygen effect** and **reoxygenation** are discussed in Chaps. 24 and 26.
  - Reoxygenation can increase tumor cell *killing* in previously hypoxic areas of tumors but does not affect well-oxygenated normal tissues.
- **Redistribution** and **repopulation** are discussed in Chap. 27.
  - Redistribution can increase tumor cell *killing* as the cells enter more radiosensitive parts of the cell cycle.
  - Repopulation increases tumor and normal cell *survival* over the course of a prolonged treatment time.
- A so-called **fifth R** is **Radiosensitivity**, which varies between different tissues and tumors.

Sublethal and Potentially Lethal Damage Repair

- There are two different types of "operationally defined" repairable damage that are measured by different assays:
  - **SLDR** and **PLDR** both contribute to the survival of cells, tissues, or tumors after irradiation.

Sublethal Damage Repair (SLDR)

- **Definition of SLD**: DNA damage that is never lethal by itself but can become lethal if combined with additional damage.
  - See "Accumulated Intertrack Damage" (Chap. 21).
- Two radiation doses must be given. Cells are given time to repair between the two doses.
- After the second dose, cells are immediately plated out to measure survival.
- **Mnemonic: SLD = split dose** experiment (see Fig. 23.5 for an example).

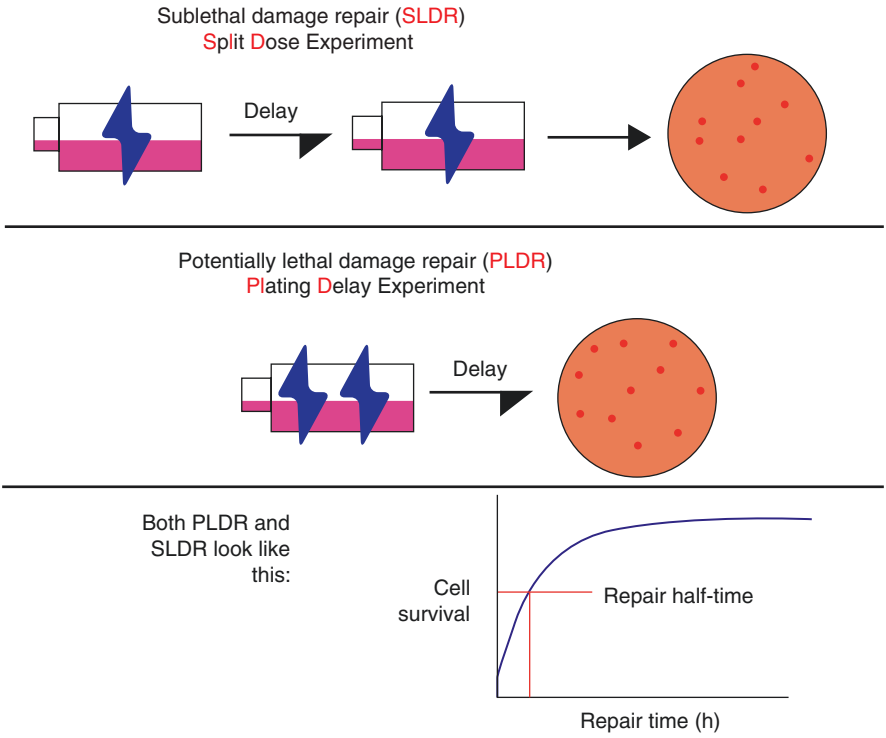

Fig. 23.5 Sublethal and potentially lethal damage are two different types of repairable damage. These are measured by "Split Dose" and "Plating Delay" experiments, respectively

Potentially Lethal Damage Repair (PLDR)

- **Definition of PLD**: DNA damage that is **lethal during cell division** but can be repaired prior to cell division.
- A single radiation dose is given.
- After irradiation, cells are given time to repair under nongrowth conditions, prior to plating out and measuring survival.
- **Mnemonic: PLD = plating delay** experiment (see Fig. 23.5 for an example).

Half-Time of Repair

- Repair occurs fairly rapidly, with a repair half-time of **~1 h** in cell culture.
- Repair times may be longer for late-responding normal tissue.
- Repair is essentially complete by **6 h** post-radiation.
  - Most twice-daily radiotherapy regimens use a minimum of **6 h** between fractions.
  - Three times daily regimens may "cheat" with a 4 h minimum, mostly for scheduling reasons.

Dose Rate

- Radiation-induced mammalian cell killing by low LET radiation (Chap. 24) has a strong dose rate dependence below 1Gy/minute and generally the "dose rate effect" is observed between 1 and 100 cGy/min in several mammalian cell lines.
- As the dose rate is reduced, with low LET radiation, mammalian cell killing is reduced and the survival curve becomes shallower (D_0 increases) and the shoulder tends to disappear.
- Resistant cells with large shoulders on their survival curves have large dose rate sparing effects (see Fig. 23.6 for an example).
- Radiation-sensitive mammalian cells and cells with DNA DSB repair defects that have nearly pure exponential survival curves with very little evidence of a shoulder have very small if any sparing by lowering dose rates below 1 Gy/minute.
- Radiation-induced mammalian cell killing by high LET (Chap. 24) radiation has very little, if any, dose rate effect due to the complexity of the DNA damage produced and the difficulty of repairing that damage by the mammalian cell DNA damage repair pathways.

Ultrahigh Dose Rate (FLASH-RT)

- Accelerators were developed in the middle of the twentieth century that were able to deliver doses of low LET electrons to cells and tissues in single nanosecond pulses.

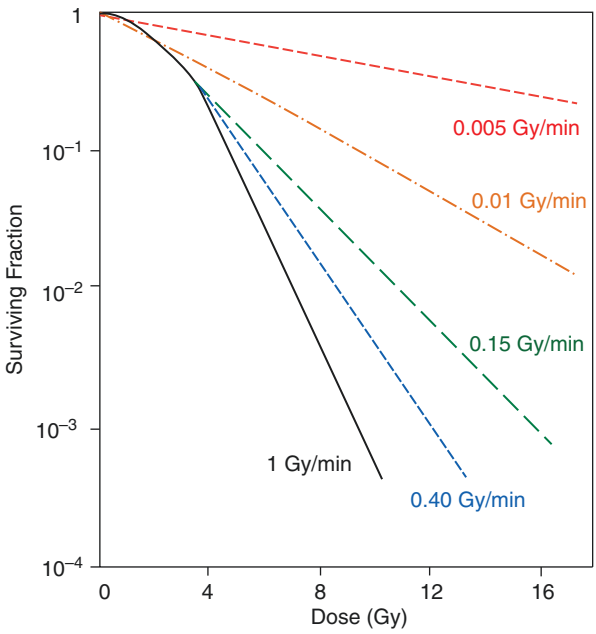

Fig. 23.6 The effect of dose rate of less than 1 Gy/min on a mammalian cell survival curve with a shoulder indicative of radiation resistance. Below 1 Gy/min results in significant sparing of low LET radiation-induced cell killing, higher survival, and flattening of the survival curve slope due to DNA repair occurring during the irradiation period to deliver various physical doses in Gy

- These ultrahigh dose rates were utilized to study the nature and kinetics of radiation-induced DNA damage and repair, and the role of oxygen in direct versus indirect effect (Chap. 24) in radiation-induced DNA damage and in cell killing in cells and tissues.
- Investigators found that if the level of dissolved oxygen was low enough in the cells or tissue being irradiated (on the order of a few percent), you could deplete all the oxygen in the cells or tissue being irradiated and only get direct effect DNA damage (i.e., 2/3 less DNA damage) per physical dose and therefore less cell killing or tissue damage would result.
- In the last several years, investigators have begun to reinvestigate ultrahigh dose rates (100–500 Gy/s) or in single nanosecond pulses now called (FLASH-RT)) and have indeed found sparing of normal tissues in the brain, abdomen, and skin for electrons, X-rays, and protons.
- Preliminary studies indicate that experimental tumors are not spared when irradiated at FLASH-RT ultrahigh dose rates and therefore this approach has the potential to improve the therapeutic ratio.

Oxygen Effect, Relative Biological Effectiveness, and Linear Energy Transfer

24

Introduction

Oxygen is one of the most effective dose-modifying agents. Oxygen causes "fixation" of radiation-induced DNA damage. The oxygen enhancement ratio (OER) is equal to the ratio of doses of radiation (hypoxic over oxic) required to achieve the same biological effect. Similarly, effectiveness of different types of radiation can be assessed by determining the ratio of doses required to achieve the same effect. This number is called relative biological effectiveness (RBE). Linear energy transfer (LET) is the density of ionizations deposited by each radiation type along its track. As LET increases, OER decreases until it becomes 1 (e.g., there is no oxygen effect). As LET increases, RBE increases up to a point (100 keV/μm), and then declines due to the "overkill effect."

Oxygen Effect

Why?

- **Oxygen Fixation Hypothesis**:
- Ionizing Radiation creates ion pairs in water.
  - Note that this is a form of **indirect action**.
  - Direct action creates ion pairs in DNA and is unaffected by oxygen.
- Within nanoseconds: Ion pairs in water react with molecules to form free radicals (**R**).
- Within microseconds: Free radicals are eliminated by sulfhydryl-containing free radical scavengers, such as glutathione (**GSH**).
- Oxygen reacts with free radicals in DNA to form peroxides (**ROO**) which **cannot be easily repaired**.
  - This is known as "oxygen fixation" (Fig. 24.1).
- Oxygen increases indirect effects of ionizing radiation if it is present during or within microseconds after irradiation.

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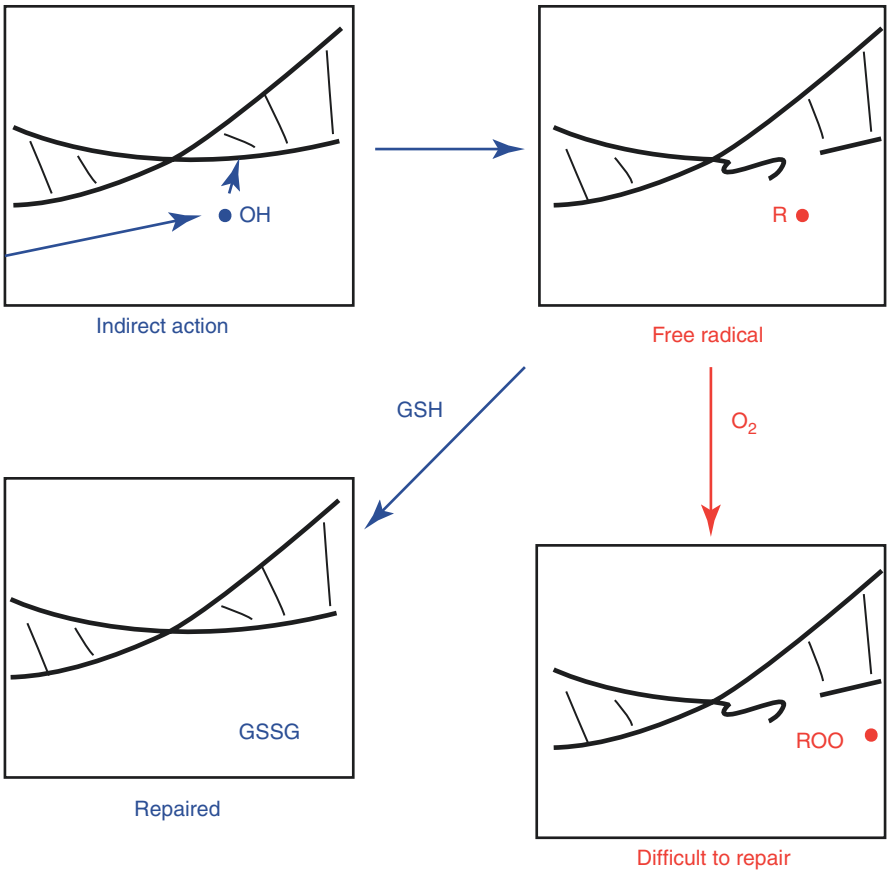

Fig. 24.1 The oxygen fixation hypothesis. Free radicals are easily repaired by antioxidants, but molecular oxygen can convert them into peroxides that are more difficult to repair

- It does not matter what the oxygen concentration is seconds pre- or postirradiation.
- Therefore, transient hypoxia is a big deal! See Chap. 26 for details.

How Much Oxygen Is Needed for the Oxygen Effect?

- The Oxygen Effect operates at very low concentrations of O_2:
  - **0.001% O_2** (0.008 mmHg): Fully anoxic, no oxygen effect.
  - **0.5% O_2** (4 mmHg): Half oxygen effect.
  - **2% O_2** (16 mmHg): Full oxygen effect, no significant difference with further increase in O_2.

- Oxygen levels for comparison:
  - **0.13% O_2** (1 mmHg): Fully hypoxic tissue.
  - **2–5% O_2** (20–40 mmHg): Venous blood.
  - **8–13% O_2** (60–100 mmHg): Arterial blood.
  - **20% O_2** (150 mmHg): Room air.
  - **100% O_2** (760 mmHg): Pure oxygen.
- Note that normal tissue should not be hypoxic!
- Even the lowest oxygen tensions in a living human are well above what is needed for full oxygen effect.
- Therefore, hypoxia protects tumors; it does not protect normal tissues.
- See Chap. 26 for a detailed discussion of hypoxia in tumors.

Oxygen Enhancement Ratio (OER)

- **OER** is defined as the **ratio of doses** that achieve the same biological endpoint (such as cell survival):

$$\mathrm{OER} = \frac{\mathrm{Dose}\ \left(\mathrm{Hypoxic}\right)\ \mathrm{to\ cause\ an\ effect}}{\mathrm{Dose}\ \left(\mathrm{Normoxic}\right)\ \mathrm{for\ same\ effect}} \tag{24.1}$$

  - Keep in mind it is a ratio of doses, not a ratio of survival or log kill or tumor control or anything else.

- A clinically relevant **OER** (for megavoltage photons) is somewhere around 3.0 (2.5–3.5):
  - In order to kill as many cells as 2 Gy of Co-60 under normoxic conditions, you would need 6 Gy of Co-60 under fully hypoxic conditions.
  - It is easy to see why hypoxia can be such a big deal for clinically relevant tumors!
- **OER** is somewhat greater at a high fraction size (~3.5) compared to that at a low fraction size (~2.5).
  - **Small fractions**: Survival curve is dominated by the most sensitive cells (G_2/M) which have the lowest OER.
  - **Large fractions**: Survival curve is dominated by the most resistant cells (S) which have the highest OER.
  - This behavior is the opposite of RBE.
- **OER** varies depending on the type of radiation:
  - Damage from **low LET** radiation is mostly mediated by indirect action and has a very large oxygen enhancement ratio (OER ~3).
  - **High LET** radiation causes more damage through direct action, which is not oxygen dependent (OER ~1) (Fig. 24.2).

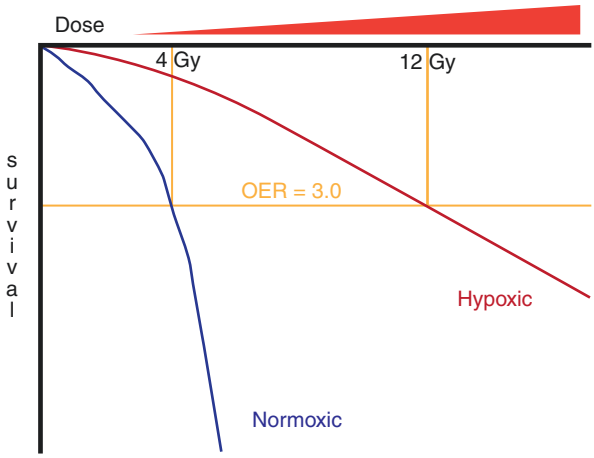

Fig. 24.2 Oxygen enhancement ratio: OER is defined as the ratio of doses that achieve the same effect, as shown by the horizontal orange line

Relative Biological Effectiveness (RBE)

- Not all radiation is created equal! 1 Gy of 1 GeV carbon ions is very different from 1 Gy of Co-60 gamma rays.
- **RBE** is defined as the **ratio of doses** that achieve the same biological endpoint:

$$\text{RBE} = \frac{\text{Dose of standard radiation to cause an effect}}{\text{Dose of test radiation for same effect}} \tag{24.2}$$

  - Keep in mind it is a ratio of doses, not a ratio of survival or log kill or tumor control or anything else.
  - Standard radiation may be defined as **250 kVp X-rays** (as in Hall and Giaccia) or **Co-60** (as in "Cobalt Gray Equivalent") (Fig. 24.3).
- At an **RBE** of 3, you need 3 Gy of standard radiation to achieve the same cell kill as 1 Gy of test radiation.
  - **RBE** is usually measured by acute effects, so it does not predict late effects (this is a big problem for neutron irradiation).
- **RBE** varies by cell type:
  - Radioresistant cells are resistant to standard radiation, so the **RBE** of high-LET radiation increases.
  - However, very radiation-sensitive cells (including cells with mutations in DNA double-strand break repair pathways) are also sensitive to standard radiation, so **RBE** of high-LET radiations is low.
- **RBE** is greatest at a small fraction size:
  - **Small fractions**: Repair predominates for standard radiation but is ineffective for high-LET radiation.
  - **Large fractions**: Repair is overwhelmed even with standard radiation.

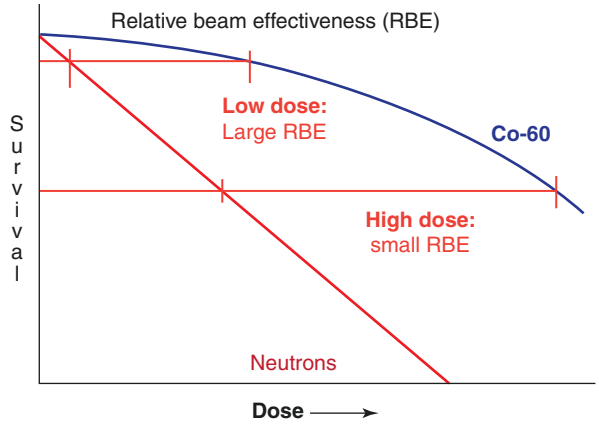

Fig. 24.3 RBE and Dose: RBE is defined as the ratio of doses that achieve the same effect, as shown by the horizontal line. RBE is greater at small fraction sizes than at large fraction sizes

  - This behavior is the opposite of **OER** (OER is greatest with large fraction sizes).
- Compare this to **Quality Factor (QF)** aka **Weighting Factor (W_R)**, which is the number used for radiation protection purposes (see Chap. 14).
  - **QF** is a conservative number and overestimates the effect of particulate radiation.
  - **QF** does not predict tumor response or normal tissue acute effects.
  - **QF** is intended as a "ballpark estimate" of normal tissue late effects, carcinogenesis and heritable risk.

Linear Energy Transfer (LET), RBE, and OER

- **LET** is a measure of how densely ionizing a radiation beam is (Fig. 24.4).
  - See Chap. 5 for a detailed discussion of **LET**.
- As **LET** increases, **RBE** increases until it reaches a peak at 100 keV/μm.
  - Decreased repair due to high density of ionizations.
  - Increased direct action, less oxygen dependent.
  - Increase in complexity of DNA damage.
  - 100 keV/μm corresponds to one ionization per 2 nm, which is the diameter of a DNA strand and is considered the optimal LET for cell killing.
- After ~100 keV/μm, **RBE** decreases with **LET** (Fig. 24.5).
  - Overkill effect: when the ionization density deposited by particles is greater than what is required to kill a cell. Therefore, the radiation kills less cells per absorbed dose.
- **OER** strictly decreases as **LET** increases.
  - LET < 1 keV/μm: OER = 2.5–3.5.
  - LET > 100 keV/μm: OER = 1.0.

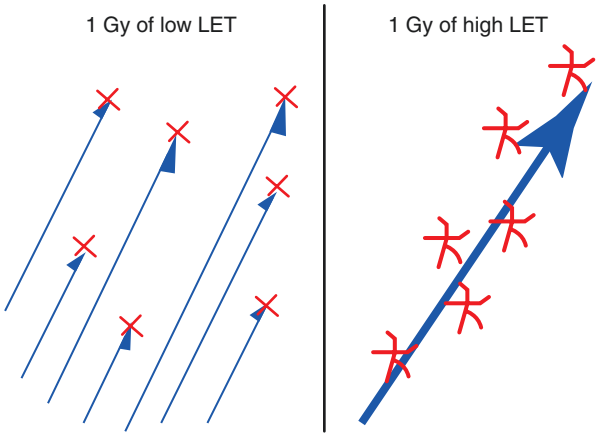

Fig. 24.4 A diagram of low LET radiation versus high LET radiation. Both deposit the same radiation dose (ionizations, *red stars*). However, the low LET ionization events are widely scattered while the high LET ionization events occur in a dense track

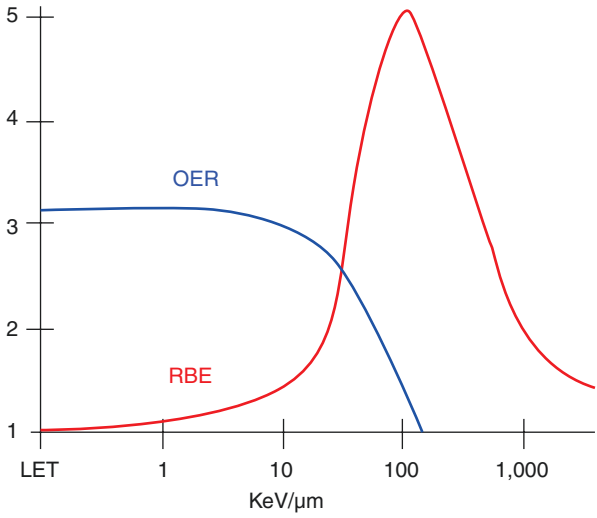

Fig. 24.5 OER and RBE versus LET: As LET increases, RBE peaks around ~100 keV/μm before it trends back down. OER strictly decreases with LET until it reaches 1 at ~100 keV/μm

- Typical LET for different forms of radiation:
- Megavoltage X, γ, e^-: **LET 0.2–0.5 keV/μm.**
- Fast protons (150 MeV): **LET 0.5 keV/μm.**
- Kilovoltage X, γ: **LET 2–4 keV/μm.**
- Slow protons (10 MeV): **LET ~ 5 keV/μm.**
- Fast neutrons and alphas: **LET ~ 100 keV/μm.**
- Heavy ions (carbon, argon, oxygen, iron, etc.): **LET 100–1000 keV/μm.**
- For carbon ions used for therapy, the **LET** can increase from the front to the back edge of the SOBP from **~20 to 100 keV/μm.**

Normal Tissue Radiation Response

25

Introduction

Radiation toxicity in normal tissues can be classified as early effects, late effects, and consequential late effects. These effects vary based on the tissue type, radiation dose, fractionation, and the volume of tissue irradiated. Parallel organs such as the lung can tolerate high doses to a small volume better than low doses to the whole organ. Serial structures such as the spinal cord can tolerate low doses to the whole organ but cannot tolerate high doses to a small volume. Two major schemes for tissue classification are the Casarett classifications and Michalowski classifications. Radiation effects on normal tissues are described in a series of paragraphs split up by organ or tissue. Toxicity observed in human patients is scored on a variety of schemas, including Late Effects of Normal Tissue, Subjective Objective Management Analytic (LENT-SOMA) and Common Toxicity Classification for Adverse Events (CTC-AE).

Types of Normal Tissue Effects

- **Early effects** usually occur within 60 days of irradiation and are due to acute cell killing.
  - These generally involve tissues with rapid cell turnover.
  - As long as enough stem cells survive to repopulate the tissue, early effects can be completely repaired over time.
- **Late effects** generally occur >60 days later and are due to effects other than acute cell killing.
  - Mechanisms include vascular damage, fibrosis, and damage to parenchymal cells in organs.
  - These generally involve tissues without rapid cell turnover, and cannot be completely repaired.

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- **Consequential late effects** are permanent tissue damage secondary to early effects.
  - These are caused by a very severe early effect that never completely heals.
  - For example, skin necrosis requiring a skin graft.

Fraction Size and Treatment Time Effects

- **Acute effects** are less sensitive to fraction size (high **α/β**) but more sensitive to overall treatment time.
  - Toxicity based on **Total Gy** and **Gy per week**.
  - Prolonging the course of radiation allows for repopulation.
- **Late effects** are more sensitive to fraction size (low α/β) but less sensitive to overall treatment time.
  - Toxicity based on **Total Gy** and **Gy per fraction**.
  - Fractionation allows for increased repair, but little or no repopulation occurs within a clinically relevant time span.
- When re-treating a previously irradiated area, keep in mind:
  - Late effects are never completely repaired. This is the concept of **remembered dose**, which decreases the tissue's tolerance to reirradiation.
  - Acute reacting tissues do not "remember" as much dose as late-reacting ones.

Stem Cells: Latency and Functional Subunits

- In a tissue with dividing stem cells and nondividing functional cells, the functional cells are largely unharmed by radiation while the stem cells are killed.
  - There is a **latency period** before any tissue dysfunction becomes apparent.
  - The **latency** time is equal to the lifespan of the functional cell affected.
- Following this, any surviving stem cells will attempt to regenerate the tissue.
- Each stem cell can only regenerate a finite volume of organ. This volume is called the **functional subunit** (FSU).
- A **structurally defined FSU** is an anatomic structure that defines a group of cells.
  - Kidneys, lungs, livers, and exocrine glands are organized into structurally defined FSUs (nephrons, bronchial trees, portal triads, etc.).
- A **structurally undefined FSU** is not an anatomic structure at all.
  - For example, stem cells in the skin can only migrate a finite distance, but this is not limited by any specific anatomic boundary.
- A **tissue rescue unit** is the minimum number of FSUs required for organ function.

Serial and Parallel Organs and Volume Effect

- In a **serial organ** (CNS, GI tract), loss of function in one part of the organ will cause the entire organ to stop functioning.

  - Therefore, there is no **threshold volume** – high dose to even a small volume can cause critical injury.
  - The probability of damage is proportional to the volume irradiated:
    If 50 Gy to spinal cord has a 1%/cm chance of myelopathy, irradiating 1 cm of cord may be reasonable, but irradiating 30 cm of cord would not be reasonable.
  - The risk of injury is dominated by the **highest dose**.
    The spinal cord can tolerate 36 Gy to the whole organ but cannot tolerate 74 Gy to one spot.
- In a **parallel organ** (kidney, lung, liver), loss of function in one part of the organ only affects that part of the organ.
  - There is a **threshold volume** effect: you can take out an entire kidney without causing renal failure if the other kidney is healthy.
  - Partial organ effect does not always correlate with whole organ function.
    For example, chest CTs after chest wall irradiation will show changes in a small slice of lung within the radiation field.
    However, the rate of symptomatic pneumonitis is very low.
  - The risk of injury is dominated by the **average dose** over the whole organ volume.
    The lung cannot tolerate 36 Gy to the whole organ but can easily tolerate 74 Gy to one spot.
- Skin and mucosa are neither serial nor parallel, but they behave clinically like **parallel** organs.
  - This is because desquamating a small area of skin is much more tolerable than desquamating a large area.

Casarett's Classification of Radiation Sensitivity

- Arranged from most sensitive (Group I) to least sensitive (Group IV).
- **Group I: Vegetative Intermitotic**
  - Divides constantly with no differentiation – like a vegetable it can always grow more of itself.
  - Includes basal epithelial cells (skin, intestinal crypts, etc.), undifferentiated hematopoietic stem cells and germ cells.
- **Group II: Differentiating Intermitotic**
  - Divides for a finite amount of cycles before differentiating into a nondividing cell.
  - Includes all of the cells that are intermediate between stem cells and differentiated cells, for example, myelocytes and spermatogonia.
- **Group III: Reverting Postmitotic**
  - A normally nondividing cell that retains the potential to divide ("revert").
  - Includes liver, kidneys, and glandular tissues such as pancreas, adrenal, thyroid, and pituitary.
- **Group IV: Fixed Postmitotic**
  - A permanently nondividing cell.

  - Includes permanent cells such as nerves and muscles, as well as short-lived differentiated cells such as neutrophils, red blood cells, and superficial epithelial cells.
- **Exceptions**:
  - **Connective tissue stroma** (fibroblasts and endothelium) are intermediate between II and III.
  - **Peripheral blood lymphocytes** are incredibly sensitive to apoptosis and are very radiosensitive despite being **Group IV**.

    Other peripheral blood cells (granulocytes, RBCs, and platelets) are very radioresistant.

    Therefore, the latency time of cytopenias after RT is based on the lifespan of the differentiated cell (Fig. 25.1).

Michalowski Classifications

- Tissues are either **hierarchical** or **flexible**.
- This model predicts the time-course of radiation toxicity.
- **Hierarchical (H-type)** tissues regenerate in a fixed pathway of **stem cell –> maturing cell –> functional cell**.
  - Radiation kills stem cells, which leads to depopulation of functional cells after a **predictable latency** time.
  - Bone marrow, intestinal epithelium, and epidermis are hierarchical tissues.
- **Flexible (F-type)** tissues have no hierarchy. Nondividing cells can be triggered to divide if needed.
  - Radiation causes cells to become unable to divide, but this does not become apparent until the cell is actually triggered to divide (may be many years later).
  - The time-course and degree of organ dysfunction are **unpredictable**.
  - Liver, thyroid, and dermis are flexible tissues.

Cytokines and Growth Factors

- Radiation induces cytokines **IL-1**, **IL-6**, and the growth factor **bFGF**. These molecules act as short-term radioprotectors.
  - **bFGF** is produced by medium-sized blood vessels but not by the smallest capillaries. This is believed to be one reason why larger blood vessels are more radioresistant than the microvasculature.
- Radiation also induces the growth factors **TGFβ** and **TNFα**, which are proinflammatory and profibrotic molecules.
  - These are involved in late fibrosis and late vasculopathy.
  - Increased serum concentrations of **TNFα** correlate with late toxicities of radiation.

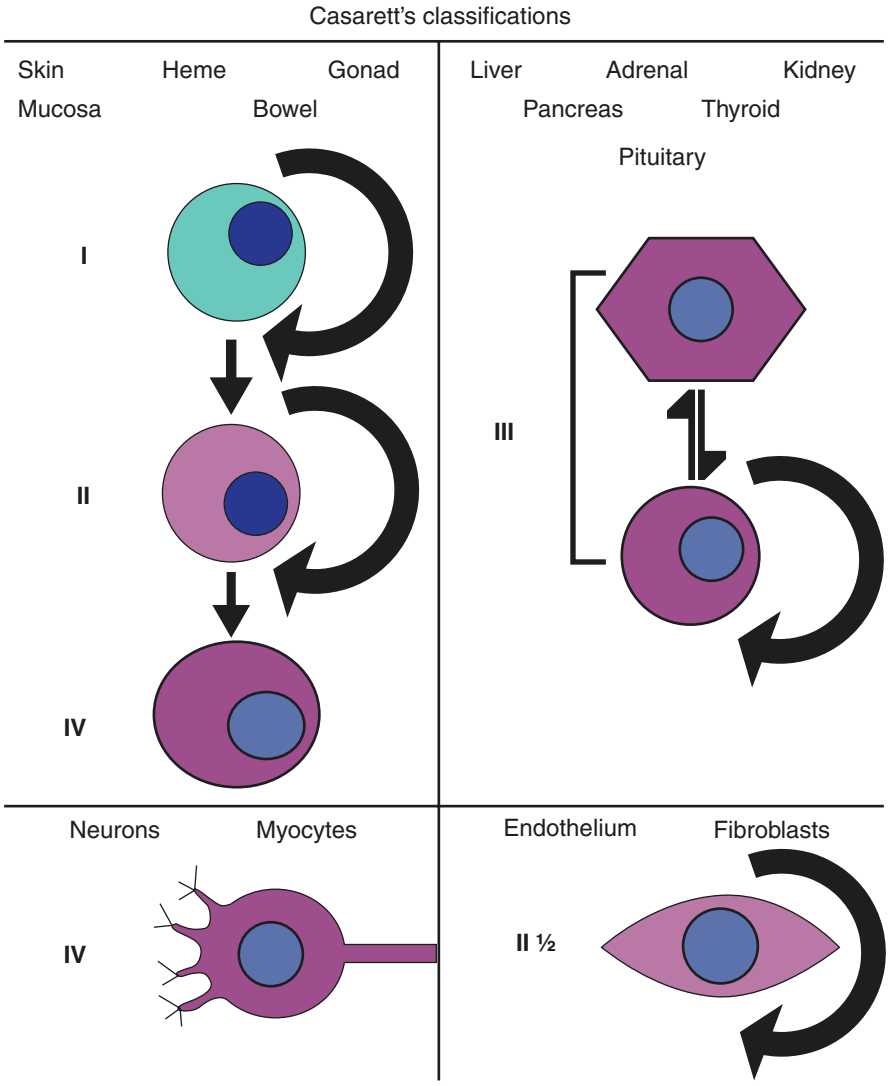

Fig. 25.1 Casarett's classifications. For skin, mucosa, gonads, bowel, and hematologic cells, the progression is from vegetative intermitotic to differentiating intermitotic to fixed postmitotic. For cells of the liver, adrenal gland, kidney, pancreas, thyroid, and pituitary, the cells are often reverting intermitotic. Nerve and muscle cells are typically fixed postmitotic by the time of birth (with few exceptions), and endothelium and fibroblasts contain elements that would be described as both reverting intermitotic and differentiating intermitotic

Normal Tissue Response: Skin

- Epidermis is an acute responding tissue while dermis is a late-responding tissue.
- Acute response: Happens in **epidermis**.
  - Erythema: due to vascular dilation and edema, can happen quickly after large single doses.
  - Desquamation: Keratinizing skin cells last for 14 days, so desquamation is generally delayed by around 14 days.
  - Epilation: due to hair follicle germinal cells, delayed by 2–3 weeks, takes 3 months to regrow.
- Late response: Happens in **dermis**.
  - Telangiectasias and fibrosis are due to chronic vascular damage and inflammation.
- Human epidermis is a fraction of a millimeter in thickness. It reacts to **surface dose** and not depth dose.
- Skin tolerance is around **60 Gy** in standard fractionation although this depends on the surface area of skin irradiated.
  - Small skin cancers can be treated with higher doses.
  - Large areas like a chest wall may experience severe acute toxicity at **50 Gy** or less.

Normal Tissue Response: Hematopoietic

- Hematopoietic stem cells (**HSCs**) are among the most radiosensitive cells in the body.
- Total Body Irradiation:
  - Hematopoietic tolerance is a $\mathbf{LD_{50}}$ of **3–4 Gy** in a single fraction, without stem cell transplant.
  - The purpose of myeloablative conditioning for stem cell transplant is to ablate the host's **HSCs**. Therefore, TBI doses exceed **HSC** tolerance.
- Partial Body Irradiation:
  - Death of **HSCs** in one part of the body induces accelerated growth and differentiation of hematopoietic cells elsewhere in the body.
  - Heavily irradiated bone marrow (>30 Gy) may never fully recover. This may be seen as abnormal marrow signal on MRI persisting for many years.
  - Extramedullary hematopoiesis (spleen, liver, soft tissue) may occur.
- Differential Effects by Cell Lineage:
  - **Lymphocytes** (including plasma cells) are the most sensitive and nadir within **hours to a few days**. Unlike the other lineages, even mature lymphocytes are radiosensitive due to apoptosis.
  - **Granulocyte** lineage is intermediate in sensitivity. Only the stem cells are killed, the differentiated cells continue their normal lifespan, with a nadir at **2–4 weeks**.

  - **Platelet** lineage is somewhat less sensitive, and platelets also nadir at **2–4 weeks**.
  - **Red blood cell** lineage is relatively radioresistant. Hemoglobin is largely unaffected by TBI unless bleeding occurs.

Normal Tissue Response: Oral Mucosa

- Mucositis occurs within ~2 weeks of RT and is a dose-limiting factor in head and neck.
- Mucositis involves sloughing of mucosal epithelium with formation of fibrinous exudate.
- Healing occurs within 1 month unless mucositis was severe enough to cause permanent alteration in function. Pain may persist a few months later.
  - Some patients with very severe mucositis end up with permanent dysphagia/odynophagia.
- Tolerance dose is somewhere around **70 Gy** (with chemo) to **75 Gy** (without chemo) with standard fractionation.
  - This value depends on site of RT, irradiated volume, and definition of tolerance (with or without feeding tube).

Normal Tissue Response: Salivary Glands

- Salivary glands include the parotids, submandibulars, and countless minor salivary glands.
- Salivary glands are considered both an acute and a late-responding tissue. Xerostomia begins within 2–3 weeks but recovers very little over time.
- Decreased xerostomia risk if bilateral parotid mean dose **<25 Gy**, or if single parotid mean dose **<20 Gy** while other parotid is treated to high dose.
- There is some evidence that RT dose to submandibular and minor salivary glands is also very important to xerostomia risk.

Normal Tissue Response: Esophagus

- Acute esophagitis occurs within 1–2 weeks of RT, is characterized by pain and dysphagia, and heals within 1–2 weeks post-RT.
- Late esophageal toxicity includes fibrosis (strictures causing dysphagia) and necrosis (ulceration).
- Esophagus tolerance depends on the intent and endpoint.
  - When treating the esophagus with concurrent ChemoRT, treatment-related mortality is higher at **64 Gy** than at **50.4 Gy** (Minsky).
  - When treating H&N or lung, risk of symptomatic esophagitis appears to depend on multiple dose–volume characteristics.

  - Circumferential irradiation is associated with higher late stricture risk; when possible, try to leave one side of the esophagus outside the high-dose field.

Normal Tissue Response: Stomach

- Acute gastritis is characterized by nausea and vomiting immediately after RT.
- Chronic gastritis, pain, delayed gastric emptying may occur months after RT.
- Ulceration and bleeding may occur months after RT.
- **Whole stomach: 45 Gy** tolerance dose.

Normal Tissue Response: Lung

- The lung is a subacute to late-responding tissue, with classic radiation pneumonitis occurring at 6 weeks to 6 months post-RT.
- Late pulmonary fibrosis may occur years post-RT.
- The lung is a parallel organ and therefore irradiated volume is extremely important. Very small lung volumes may be treated to very high doses without toxicity, as in SBRT.
- Pneumonitis risk increases gradually with increasing lung dose.
  - There may be a small risk even at low doses (i.e., whole breast irradiation) and a much larger risk at higher doses.
- Therefore, there is no single set of lung constraints. Depending on the treatment site and intent, different lung tolerances may be used.
  - **V5 (bilateral) < 70%.**
  - **V20 (bilateral) < 40%.**
  - **V20 (bilateral) < 30%.**
  - **V20 (ipsilateral) < 30%.**
  - **Mean lung dose < 20 Gy.**
- **Whole lung** irradiation of **12 Gy in 8 fractions** is tolerable in children with metastatic tumors. However, the same dose of **total body irradiation** is associated with pneumonitis and pulmonary fibrosis, so lung blocks may be used during TBI.
- Patients with other comorbid lung injury (COPD, bleomycin exposure, pneumonectomy) have a higher risk of radiation pneumonitis.

Normal Tissue Response: Kidney

- The kidney is a late-responding tissue, with a gradual decline in renal function for many years postirradiation.
- Kidneys are parallel organs and irradiated volume is very important.

- Kidney tolerance is very dependent on comorbid kidney injury, such as chemotherapy, hypertension, diabetes, and age.
  - Plenty of cancer patients have kidney failure even without any radiation to kidneys!
- Whole kidney $\mathbf{TD_5}$ = 15–18 Gy (QUANTEC).
- Whole kidney $\mathbf{TD_{50}}$ = 28 Gy (QUANTEC).

Normal Tissue Response: Liver

- The liver has an extremely high regenerative capacity. 2/3 of the liver can be surgically removed and the remaining liver will regenerate to full size.
  - Therefore, there is a very strong dose–volume effect.
  - Liver failure is much less likely if some part of the liver is spared (completely outside field).
- Liver is a late-responding tissue, taking years to manifest any symptoms of injury.
  - Except for patients with preexisting cirrhosis.
  - Most primary liver tumors occur in cirrhotic patients.
- Whole liver $\mathbf{TD_5}$ = 30–32 Gy in a healthy liver, 28 Gy with Child-Pugh A cirrhosis (QUANTEC).
- Whole liver $\mathbf{TD_{50}}$ = 42 Gy in a healthy liver, 36 Gy with Child-Pugh A cirrhosis (QUANTEC).

Normal Tissue Response: Bladder

- Bladder is a late-responding tissue with a latency of several months.
- Loss of bladder surface cells causes irritation and proliferation of deeper stromal cells such as fibroblasts.
- This leads to irritability, fibrosis, and progressive reduction in bladder capacity.
- **Whole bladder RT:** Tolerance dose 65 Gy.
- **Prostate:** $V_{65} < 50\%$, $V_{70} < 35\%$, $V_{75} < 25\%$, $V_{80} < 15\%$.

Normal Tissue Response: Heart

- Late-responding tissue, toxicity can be delayed by years to decades.
  - Very sensitive to fraction size.
- Pericarditis and cardiomyopathy depend on total heart volume irradiated, whole heart RT can result in a subacute pericarditis.
  - Whole heart dose of **26 Gy**: 15% risk of pericarditis.
  - When designing mediastinal fields or mantle fields for lymphoma, try to block heart to some extent.

- Cardiotoxic chemotherapy (Adriamycin) can further increase the risk of cardiac morbidity.
- Accelerated atherosclerosis is due to the combination of RT to coronary vessels, and comorbid risk factors like HTN, HLD, tobacco.
  - Advise patients in risk factor reduction.
  - Coronary vessels may be contoured as an additional structure for 3D planning.

Normal Tissue Response: Bone and Cartilage

- Late toxicity, different for children and adults.
- Irreversible growth suppression occurs after doses of **10–20 Gy** in children.
  - Irradiating a partial vertebral body is discouraged due to risk of scoliosis from imbalanced growth.
- Osteoradionecrosis or fracture may occur in any bone receiving **>65–70 Gy**. This toxicity may be delayed by months to years.

Normal Tissue Response: CNS

- Spinal cord is more sensitive than brain.
- Very sensitive to fraction size – **CNS α/β is 1–2**.
- Acute: Transient demyelination (Somnolence syndrome, Lhermitte sign).
- Late: Vascular changes (microinfarcts, microhemorrhage, moyamoya), cognitive dysfunction, myelopathy (cord), or necrosis (brain).
- Spinal cord tolerance is around **50 Gy** (without chemo), **45 Gy** (with chemo), at standard fractionation.
- Brain can tolerate **72 Gy** to small volumes.
- Brainstem can tolerate **54–60 Gy** (the exact number is controversial).

Normal Tissue Response: Peripheral Nerves

- Brachial plexus tolerance is around **60 Gy**.
- Injury to the brachial plexus leads to irreversible pain and weakness of the upper extremity, with a several month to few year latency period.
- Other peripheral nerves may be injured by irradiation but are less well studied.

Normal Tissue Response: Gonads

- The testes are one of the few organs in the body that are more sensitive to fractionated RT than to single fractions.
- Sperm production is extremely radiosensitive; **0.1 Gy** can decrease sperm count and **6 Gy** can cause permanent sterility.

  - Sperm count takes **~74 days** to nadir.
  - Radiation is not a reliable form of sterilization; there are case reports of men fathering children after **8 Gy TBI and stem cell transplant**.
- Larger doses (**≥20 Gy**) are required to decrease testosterone production.
- The ovaries are also very radiosensitive, but the dose required to cause clinical symptoms depends on age.
  - Older women have fewer oocytes remaining, so even tiny doses (**2 Gy**) can cause immediate ovarian failure.
  - Younger women (teenage girls) may require over **12 Gy** to cause ovarian failure.
  - Radiation-induced ovarian failure behaves clinically like any other source of ovarian failure (surgical, chemo-induced, or natural menopause).

Normal Tissue Response: Genitalia

- The skin on vulva and penis are similar to skin elsewhere but due to location and moisture, any skin reaction is very unpleasant.
- The vagina is remarkably radioresistant, and can generally exceed **100 Gy** with LDR brachytherapy before developing ulcerations or fistulas.

Scoring Systems for Adverse Events

- In the modern era, adverse event scores typically use a 5-point scale, somewhat analogous to ECOG performance status:
  - **Grade 0:** No adverse event
  - **Grade 1:** Asymptomatic or mild symptoms not requiring intervention
  - **Grade 2:** Moderate symptoms requiring noninvasive intervention, not causing hospitalization or disability
  - **Grade 3:** Severe symptoms but not urgently life-threatening, causing hospitalization or disability
  - **Grade 4:** Life-threatening consequences requiring urgent intervention
  - **Grade 5:** Death
- **Like cancer staging systems, adverse event scoring systems have evolved over time.**
  - Late Effects of Normal Tissue, Subjective Objective Management Analytic **(LENT-SOMA)** (1992): Grade 5 was "complete loss of function," not death.
  - RTOG Common Toxicity Criteria **(CTC)** (1995): Originally developed by radiation oncologists. Separate scoring systems for early and late toxicities.
  - Common Toxicity Criteria **(CTC) v2.0** (1999): Added chemotherapy toxicities.
  - Common Toxicity Criteria for Adverse Events **(CTC-AE) v3.0** (2003): Added "adverse events" which include nontreatment-related injury and illness.

  - Common Toxicity Criteria for Adverse Events **(CTC-AE) v4.0** (2009): Added more detail, tried to decrease vagueness/subjectivity.
  - Common Toxicity Criteria for Adverse Events **(CTC-AE) v5.0** (2017): Harmonized terminology with MedDRA, an international naming convention that allows, for example, an English language clinical trial to be translated into Japanese without losing specificity.
- One drawback common to all toxicity scoring systems is that clinical management decisions can affect toxicity grading.
  - Two patients are wheezing and mildly short of breath, one gets an inhaler and one does not, both eventually get better.
  - The first patient is scored as "Grade 2" pulmonary toxicity while the second is "Grade 1" even though they had the same toxicity.
  - In theory, an unblinded investigator could bias their toxicity scores downward by being less aggressive with symptom management.

Tumor Microenvironment

26

Introduction

Tumor growth is frequently limited by oxygen supply. Tumor cells may be chronically hypoxic if they are too far away from blood vessels or transiently hypoxic if a blood vessel is temporarily blocked. Tumors secrete angiogenesis factors, such as VEGF, to increase their blood supply. Hypoxic tumor cells are resistant to radiation. Tumor hypoxia may be measured with various invasive and noninvasive methods. During fractionated irradiation, reoxygenation decreases radioresistance. The classic hypoxia signaling pathway is mediated by HIF-1. Tumor hypoxia may predispose cells to genomic instability, invasion, and metastasis.

Tumor stem cells are a small percentage of the tumor that accounts for most of its clonogenic activity and resistance to therapy. If a course of therapy does not eradicate the tumor stem cells, the tumor will recur.

Tumor Vasculature

- One of the most important limiting factors in a tumor's growth is its blood supply.
  - Many tumors grow in cords surrounded by or partially surrounding normal stroma. This allows them to take advantage of normal blood vessels.
  - Many tumors secrete growth factors that promote the in-growth of new blood vessels.

    This process is known as **angiogenesis**.

    VEGF is the most famous angiogenic growth factor and is the target of bevacizumab (Avastin) and other antiangiogenic drugs.
- Tumor vasculature is "leaky," poorly organized, and less effective than normal blood vessels.
  - The **normalization hypothesis** states that antiangiogenic therapy can actually improve tumor perfusion by removing abnormal, leaky vessels.

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  - Therefore, antiangiogenic therapy may actually increase oxygenation and drug delivery to tumors.
- Many tumors have necrotic regions where oxygen pressures are so low that tumor cells die of anoxia.
- Hypoxia greatly decreases the efficacy of low-LET radiation, as discussed in Chap. 24.

The Thomlinson–Gray Hypothesis

- In **1955**, Thomlinson and Gray found that human lung cancers grew in **tumor cords** surrounded by vascularized normal stroma.
  - All tumors larger than ~200 μm had a necrotic core.
  - Only the outermost 100 μm of any cord contained viable cells, while the inner portion was necrotic (Fig. 26.1).
- The **Thomlinson–Gray hypothesis** states that the thickness of viable tumor is limited by the diffusion of oxygen.
  - The diffusion distance of oxygen is ~70 μm, after which oxygen tension drops off dramatically.
  - Between 70 and 100 μm, cells are chronically hypoxic.
  - After 100 μm cells begin to die from anoxia. This causes a necrotic core to develop.
- Since the 1950s, many oxygen-measuring experiments have confirmed the Thomlinson–Gray hypothesis.

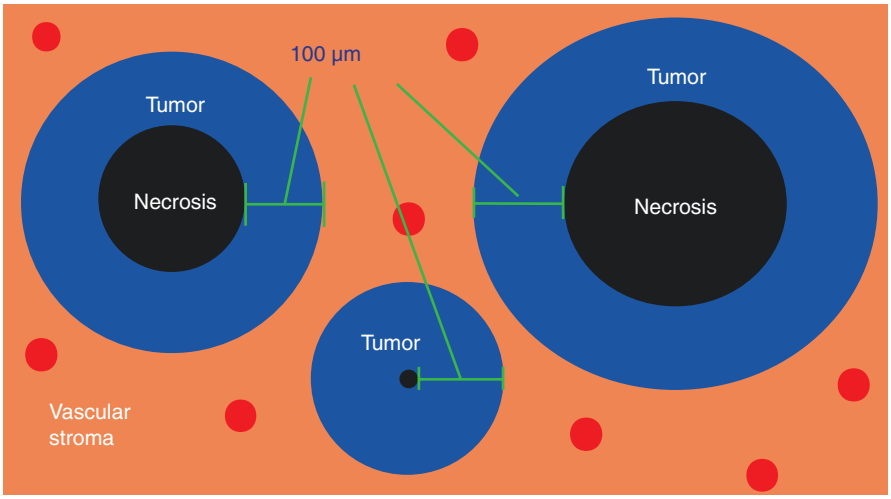

Fig. 26.1 The Thomlinson–Gray hypothesis. Tumors grow in cords surrounded by normal stroma. Regardless of the size of the cord, only the outermost ~100 μm contain viable cells. This is due to the diffusion distance of oxygen

Mixed Normoxic/Hypoxic Survival Curves

- Like a human tumor, a tumor in an experimental animal will contain both normoxic and hypoxic tumor cells.
- Irradiating the animal tumor and then plating out cells to measure survival will result in a curve that looks like this (Fig. 26.2).
- This "biphasic" survival curve can be broken down into two different regions:
  - In the low-dose region, normoxic cells outnumber hypoxic cells, and so it looks more like a normoxic survival curve.
  - In the high-dose region, normoxic cells are all killed by the radiation, so it looks more like a hypoxic survival curve.
- The **hypoxic fraction** can be estimated by extrapolating the hypoxic portion of the curve back to zero dose.
  - If the curve crosses the Y-axis at SF = 0.05, then approximately 5% of the tumor cells are hypoxic.
- The **OER** can be estimated by the ratio between the D_0 in the high-dose region and D_0 in the low-dose region (Powers–Tolmach method).
  - For example:
  - Low-dose D_0 = 1.1 Gy.
  - High-dose D_0 = 2.6 Gy.
  - OER = 2.6/1.1 = 2.4.

Direct Measurement of Hypoxia

- **Oxygen probes** are microscopic electrodes placed into tumors to directly measure oxygen pressure.
  - The Eppendorf probe is the "gold standard" of oxygen measurement. It is very accurate and can be moved around in tissue or tumors to measure oxygen at different points.

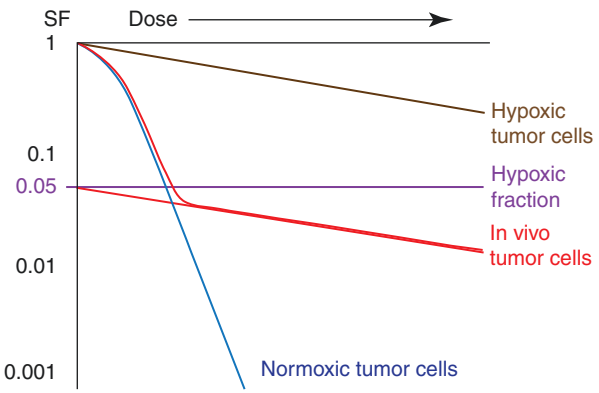

Fig. 26.2 In vivo survival curve: tumors in an experimental animal were irradiated and then plated out to count determine cell survival (*red*). The resulting survival curve can be thought of as the sum of two curves, one for normoxic tumor cells (*blue*) and one for hypoxic tumor cells (*brown*)

  - However, this is inherently invasive – you're basically sticking needles into multiple points of your specimen.
    Difficult and painful for actual patients!
- **Hypoxia markers** include exogenous and endogenous chemicals that exist under hypoxic conditions.
  - **2-Nitroimidazole drugs** (**pimonidazole, EF5**) form macromolecular adducts only under hypoxic conditions. These adducts can be stained by **IHC**.
  - **CA9** and **HIF1** are endogenous biomolecules that are part of the hypoxia response. These can also be stained by **IHC**.
    However, these molecules can also be upregulated or mutated in non-hypoxic conditions.
- **DNA damage assays** can be performed immediately after irradiation. Hypoxic cells suffer less damage.
- **Radiotracer imaging** can be performed using radiolabeled compounds that localize to hypoxic or oxic areas:
  - **Oxygen-15 PET** is the gold standard of oxygen imaging, but **O-15** has a half-life of 2 min, so it is very expensive and difficult to use.
  - "Hypoxic PET markers" such as **F-MISO**, **F-EF5**, **Cu-ASTM**, and **I-IAZA** localize to hypoxic regions, but may not correlate as precisely with oxygen levels.

Transient and Chronic Hypoxia

- Tumor vasculature is unstable. Blood vessels can occlude, congest, or otherwise stop working.
- Cells supplied by temporarily blocked blood vessels experience **transient (acute) hypoxia**.
  - These cells are radioresistant due to hypoxia (remember that tumor cells only need to be hypoxic during or for a few milliseconds after irradiation to be rendered resistant).
  - However, once the transient hypoxia goes away, the cells are fully oxygenated and healthy.
- Cells too far away from any blood vessels experience **chronic hypoxia**.
  - These cells are also radioresistant, but may be weakened or killed by hypoxia.
  - Alternatively, hypoxia may make them more prone to mutation and metastasis.
  - Chronically hypoxic cells can oxygenate one of two ways:
    Angiogenesis: growth of new vessels.
    Tumor shrinkage bringing existing vessels closer.

Reoxygenation After Irradiation

- **Reoxygenation** is one of the **Four Rs** of fractionation (Fig. 26.3).
- Reoxygenation has been extensively studied in animal tumors.

Fig. 26.3 Time scale of reoxygenation. After a radiation dose sufficient to kill normoxic cells but not hypoxic cells, only the hypoxic cells will remain. Reoxygenation occurs within hours for acute hypoxia but takes days to reverse chronic hypoxia

- Reoxygenation happens in **two phases**:
  - Fast component: occurs within 1 h to a few hours.
  - Slow component: takes several days.
  - This is believed to be due to **acute** and **chronic** hypoxia, respectively.
- Some tumors reoxygenate quickly and completely, while other tumors reoxygenate slowly and incompletely.
- **During a course of fractionated RT**:

  - A tumor that completely reoxygenates between fractions will display similar radiosensitivity during the entire course of radiation.
  - A tumor with incomplete reoxygenation will become more and more hypoxic as additional fractions of radiation are given. This greatly decreases radiosensitivity.
- The doses of fractionated RT required to cure a completely hypoxic tumor are clinically impractical, so reoxygenation is vital to the success of radiotherapy.

Hypoxia and Tumor Progression

- Multiple clinical studies have shown that tumor hypoxia correlates strongly with local failure, distant metastasis, and cancer-related death.
  - This occurs even in cancers treated with surgery alone! Therefore, it is not purely a function of radioresistance.
- There are at least three mechanisms by which hypoxia drives tumor aggressiveness.
  - **Genomic instability**:
    The combination of hypoxia and reoxygenation induces mutation and suppresses DNA repair, causing genomic instability.
    Cells deficient in apoptosis are better at surviving hypoxia. They are also more likely to mutate because they do not die when DNA is damaged.
  - **Hypoxia-induced genes**:
    HIF-1, **NF-κB**, **CREB,** and other oncogenes are strongly induced by hypoxia.
    These genes activate pathways for surviving and adapting to hypoxia, including angiogenesis and tissue remodeling (invasion).
  - **Metastasis**:
    Hypoxia dramatically increases the metastatic potential of tumor cells.

Hypoxia Inducible Factor 1 (HIF-1)

- **HIF-1** is the signaling molecule responsible for the classic hypoxia signaling pathway.
- **HIF-1** consists of two subunits, **HIF-1α** and **HIF-1β**. Out of these two, **HIF-1α** is actively regulated.
- Under normoxic conditions, **HIF-1α** is constantly degraded:
  - **HPH** hydroxylates (requires O_2).
  - **VHL** ubiquinates, targeting **HIF-1α** for degradation.
- Under hypoxic conditions **HIF-1α** accumulates and dimerizes with **HIF-1β**. This activates downstream pro-angiogenesis and pro-growth genes (Fig. 26.4).
- Loss of **VHL** can also activate **HIF-1**:

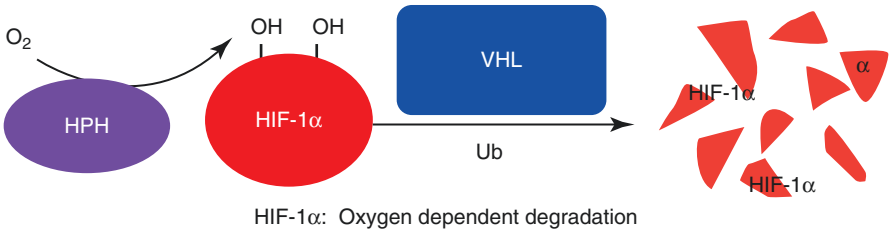

Fig. 26.4 HIF-1 regulation. Under normal circumstances, HIF-1α is continuously degraded in an oxygen-dependent manner. When oxygen is depleted, HIF-1α is no longer degraded and it accumulates

  - This causes **von Hippel Lindau (VHL)** syndrome, which includes multiple malignant and benign tumors such as retinal angiomas and renal cell carcinoma.

Tumor Composition in Patients

- Most radiobiological and animal models assume that a tumor is composed of a clone of identical tumor cells.
- However, all human tumors, especially larger ones, have heterogeneous populations of tumor cells with different mutations.
  - When a tumor recurs after a complete response, it may be due to a very small number of very resistant cells.
- The **tumor stem cell hypothesis** was proposed to explain this phenomenon. According to this hypothesis:
  - Most of the clonogenic activity of a tumor comes from a small number of cells, the tumor stem cells.
  - Tumor stem cells are relatively resistant to therapy.
  - A course of treatment can eradicate the non-stem cells in a tumor without eradicating the stem cells. This appears to be a "complete response" as the stem cells are too small to be clinically detectable.
  - However, these surviving resistant tumor stem cells can eventually regrow into a recurrent tumor.
- Besides tumor cells, human tumors also contain many host cells, including vascular and stromal elements, plus immune cells. **Tumor stromal elements** include cancer-associated fibroblasts (CAFs), mesenchymal stromal cells, and vascular endothelial cells all embedded with the tumor cells in a complex extracellular matrix or (ECM) that makes up the tumor microenvironment.
  - **Cell signaling between tumor cancer cells and tumor stromal cells** is now thought to play a role in chemotherapy and radiation resistance.
  - Even cytotoxic chemotherapy and radiation therapy may have some part of their effectiveness mediated by immune effects.

- Immunotherapy and antiangiogenic therapy work on host cells rather than tumor cells.
- Tumor cells may express molecules that evade or suppress the immune system.
- The "in situ vaccine" hypothesis suggests that when a tumor is treated by radiation or chemotherapy, radiation-damaged tumor cells provoke a stronger immune response than intact tumor cells. Investigators have proposed that carbon ion heavy ion therapy (Chap. 32) may induce an enhanced radiation immune response.
- The "abscopal effect" is immune-mediated regression of tumor sites outside of the radiation field (for example, you irradiate a lung metastasis and a pelvic lymph node shrinks).
- Concurrent radiotherapy and immunotherapy (ipilimumab, pembrolizumab, etc.) may enhance the radiation-induced immune response. See Chap. 31.

Cell and Tissue Kinetics

27

Introduction

The response of cells to low LET radiation is often dependent upon phase of the cell cycle at the time of irradiation, but the response of tumors and normal tissue is dependent on other additional parameters such as growth fraction and cell loss. G2/M phase cells are most radiosensitive, while late S-phase cells are most radioresistant. The cell cycle can stop at various checkpoints if DNA damage is detected; progression of cells into S phase or mitosis is usually delayed in normal cells if DNA is damaged. Flow cytometry can be used to measure the proportion of cells in various phases of the cell cycle. This may be used to calculate cell cycle time, growth fraction, cell loss factor, doubling time, and potential doubling time of tumors. Cell repopulation can counteract cell killing during a prolonged course of radiotherapy. On the other hand, redistribution allows cells to progress to a more sensitive phase of the cell cycle, increasing cell killing after administration of subsequent fractions of IR.

Cell and Tissue Kinetics: Why Do We Care?

- **R**edistribution and **R**epopulation are two of the four "**R**s" of radiobiology (next).
- **R**edistribution between different parts of the cell cycle can cause different effects depending on dose-rate and fractionation.
- **R**epopulation simply increases cell survival during a protracted course of treatment. Some tumors and normal tissues repopulate faster than others.

The "4 Rs" of Radiobiology

- **R**epair
- **R**eoxygenation

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https://doi.org/10.1007/978-3-030-61899-5_27

- **R**edistribution
- **R**epopulation
- The "fifth **R**" is **R**adiosensitivity.

Definitions

- **G_1**: Gap phase 1, DNA is unduplicated.
- **S**: Synthesis phase, DNA is being duplicated.
- **G_2**: Gap phase 2, DNA is fully duplicated.
- **M**: Mitosis phase, chromosomes condense, the nucleus, and cell divides.
- **T_C**: Cell cycle time (total duration of all phases).
- **T_{G1}**: G_1 phase duration.
- **T_S**: S phase duration.
- **T_{G2}**: G_2 phase duration.
- **T_M**: M phase duration.
- **MI**: Mitotic index.
- **LI**: Labeling index.
- **λ**: Cell distribution correction factor,
- **T_{vol}**: Tumor volume doubling time.
- **T_d**: Tumor diameter doubling time.
- **T_{pot}**: Potential doubling time of tumor.
- **GF**: Growth fraction.
- **CLF** (**ϕ**): Cell loss factor.

Molecular Biology of the Cell Cycle

- The cell must pass through **checkpoints** to continue through the cell cycle.
- Each checkpoint is governed by **Cdk-Cyclin** complexes and their inhibitors.
- These regulatory molecules change the amount and activity of other proteins, leading to cell cycle progression.
  - **G_1/S**: **Cyclin D, Cdk4/6**
  - **G_1/S**: **Cyclin E, Cdk2**
  - **S**: **Cyclin A, Cdk2**
  - **G_2/M**: **Cyclin B, Cdk1** (Fig. 27.1)
- The **G_1/S** checkpoint is frequently inactivated in human tumors:
  - The **Cyclin D/cdk4/6** complex is inhibited by **p21** and **p15/p16** (**INK4A**). Mitogenic signals cause Cyclin D activation.
  - The activated **Cyclin D/cdk4/6 complex** partially phosphorylates and activates the retinoblastoma tumor suppressor **Rb**, which leads to release of the **E2F** transcription factor family.
  - Release of **E2F** leads to transcription of **Cyclins E and A**, and genes involved in DNA synthesis.

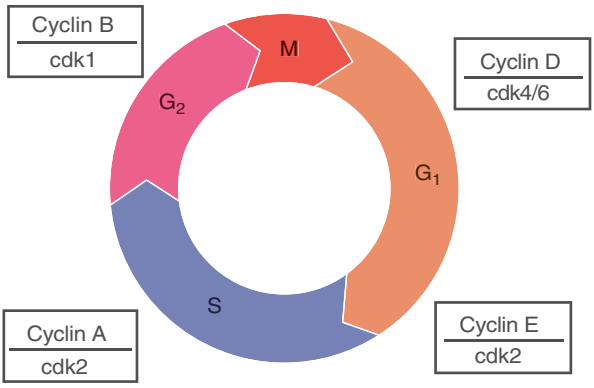

Fig. 27.1 The cell cycle. The cell has checkpoints regulated by the Cdk-Cyclin complexes that respond to other signals in the cell

  - **Cyclin E/Cdk2** and **Cyclin A/Cdk2** complexes further phosphorylate **Rb**, leading to transition into and through **S** phase.
  - **p53** blocks the **G_1/S** transition by induction of **p21** in response to DNA damage or other cellular stress.
- **Rb** or **p53** are frequently defective in tumors. They may be directly mutated or may be inhibited by other pathways.
  - This allows for uncontrolled entry into S phase.
- The **G2/M** cell cycle transition is regulated by the **Cyclin B/Cdk1** complex, which phosphorylates histone H1 and nuclear lamins leading to chromosome condensation and dissolving of the nuclear membrane in preparation for mitosis.
  - The **G2/M** checkpoint can also be induced by p21 binding.
  - It is important to remember that the **G2/M** checkpoint remains intact in most cancers.

Imaging the Cell Cycle

- **Light microscopy**:
  - Can detect **M**-phase cells by morphology and chromosome condensation
  - Cannot tell the difference between **G_1**, **S**, and **G_2**
  - **Mitotic index (MI) = % of cells in M phase**
- **^{3}H-Thymidine**:
  - Tritium (**^{3}H**) is a low-energy (**19 keV**) beta emitter commonly used in the laboratory. It is detected by autoradiography.
  - Culturing cells in ^{3}H-Thymidine will label cells in S phase as it is readily incorporated in replicating DNA.
  - **Labeling index (LI) = % of cells in S phase**.
- Microscopy and autoradiography of **^{3} H-Thymidine**-labeled cells can be used to measure **MI** and **LI** simultaneously.

Cell Cycle Kinetics: Measuring T_M and T_S (Fig. 27.2)

- Cells are unevenly distributed throughout the cell cycle because cells double during mitosis.
  - Therefore, we introduce a correction factor λ:

$$MI = \frac{\lambda \times T_M}{T_C}; T_M = \frac{\lambda \times MI}{T_C} \tag{27.1}$$

  - Typically, $\lambda \approx 0.693$ for M phase.
- The same applies to **LI** and T_S:

$$LI = \frac{\lambda \times T_S}{T_C}; T_S = \frac{\lambda \times LI}{T_C} \tag{27.2}$$

  - The value of **λ** for **S phase** can vary, but is <1.

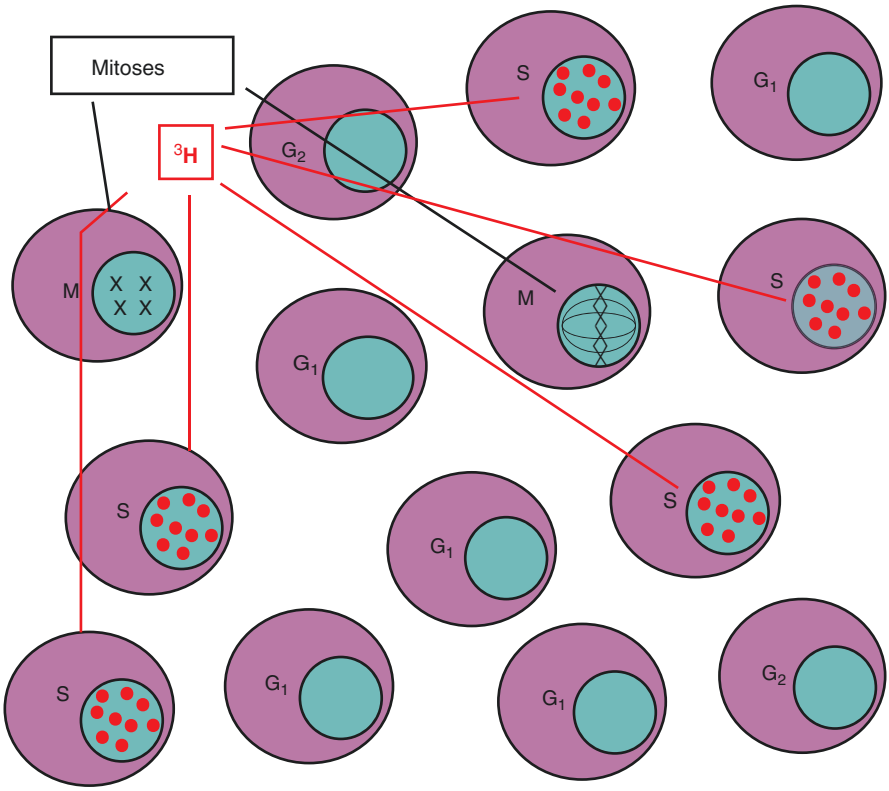

Fig. 27.2 Light microscopy can be used to view cells in mitosis and therefore measure the mitotic index. The addition of tritiated thymidine allows cells in S phase to be imaged by autoradiography, permitting measurement of the labeling index

- Using the above two equations, you can measure $\mathbf{T_M}$ and $\mathbf{T_S}$ quite easily.
- On average, $\mathbf{T_S}$ is around 1/3 of the cell cycle.

Cell Cycle Kinetics: Measuring T_C, T_{G1}, T_{G2}

- **Percent-labeled mitosis over time**:
  - All of the labeled cells are initially in **S phase**, so no mitoses are labeled.
  - Over time, the labeled cells will move into **M phase**, and all of the mitoses are labeled.
  - After a while the labeled cells progress through **G1**, **S**, and **G2**. No mitoses are labeled.
  - If you wait long enough, they will go through a second **M** phase.
- Much more laborious and cumbersome than flow cytometry, therefore rarely used any more.

Cell Cycle Measurement: Flow Cytometry

- **Flow cytometry** uses fluorescent colors and lasers to rapidly count and sort cells.
  - Cells may be fixed and labeled with a fluorescent dye or antibody conjugated to a fluorescent probe.
- It can measure cell cycle kinetics much faster than light microscopy and autoradiography.
- **DNA content (measurement of cell cycle distribution)**:
  - Cells are stained with propidium iodide (**PI**), a dye which binds DNA stoichiometrically.
  - The flow cytometer measures the amount of dye bound to DNA in individual cells. A distribution may be obtained.
  - Peaks in the cell cycle distribution appear at **G1** (DNA not yet replicated) and **G2/M** (fully replicated DNA), with **S** phase having an intermediate DNA content.
- **S-phase labeling**:
  - Cells are stained with bromodeoxyuridine (**BrdU**), which is incorporated into newly synthesized DNA of S-phase cells only.
  - S-phase cells labeled with BrdU are detected based on the fluorescence of anti-BrdU antibodies (Fig. 27.3).

Cell Cycle Parameters

- $\mathbf{T_S}$, $\mathbf{T_{G2}}$, and $\mathbf{T_M}$ vary relatively little among mammalian cells.
  - $\mathbf{T_S}$ = 6–8 h.
  - $\mathbf{T_{G2}}$ = 3–4 h.
  - $\mathbf{T_M}$ = 1 h.

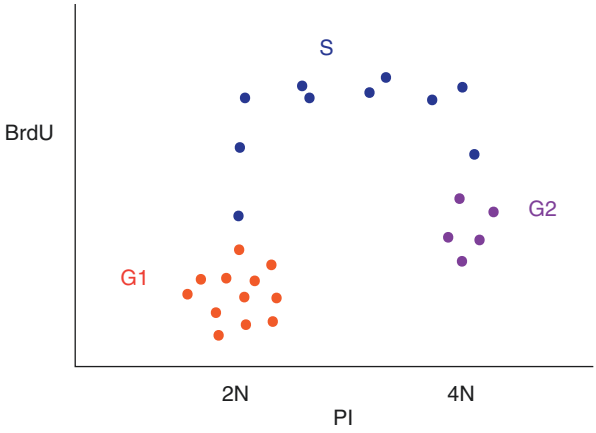

Fig. 27.3 Example of bivariate flow cytometric analysis of propidium iodide and bromodeoxyuridine staining to measure cells in G1, G2/M, and S phases

- The time $\mathbf{T_{G1}}$ is much more variable, as noted below:
  - **CHO** hamster cells have a $\mathbf{T_{G1}} = 1$ h.
  - **HeLa** human tumor cells have a $\mathbf{T_{G1}} = 11$ h.
  - Slow-growing human tumor cells can have a $\mathbf{T_{G1}}$ of several days.

Tissue (Tumor) Kinetics

- In a tissue (or tumor), not every cell is actively cycling. Some cells are quiescent, senescent, or dying.
- **Growth fraction (GF)** = % of cells that are cycling.
  - Example numbers are 90% for lymphoma, 40% in squamous, and 6% in adenocarcinoma.
- **Cell loss factor (CLF, ϕ)** is the percent of newly produced cells that die or fail to continue dividing.
  - Most human tumors have a ϕ of around 77%.
  - Tumors with a low ϕ may be more resistant to cell death, suggesting possible resistance to therapy.
- **Potential doubling time ($\mathbf{T_{pot}}$)** is defined as the time for tumor volume doubling in the absence of cell loss.
- **Volume doubling time ($\mathbf{T_{vol}}$)** is the observed time for tumor volume doubling:

$$T_{pot} = \frac{T_C}{GF}; T_{vol} = \frac{T_{pot}}{1-\phi} \tag{27.3}$$

- **Diameter doubling time ($\mathbf{T_d}$)** is equal to **3× $\mathbf{T_{vol}}$** (Fig. 27.4).
  - One diameter doubling = three volume doublings.
  - Two tumors with the same volume doubling time may have very different kinetics:

    A tumor with fast $\mathbf{T_{pot}}$ and large **ϕ** grows quickly and responds quickly.

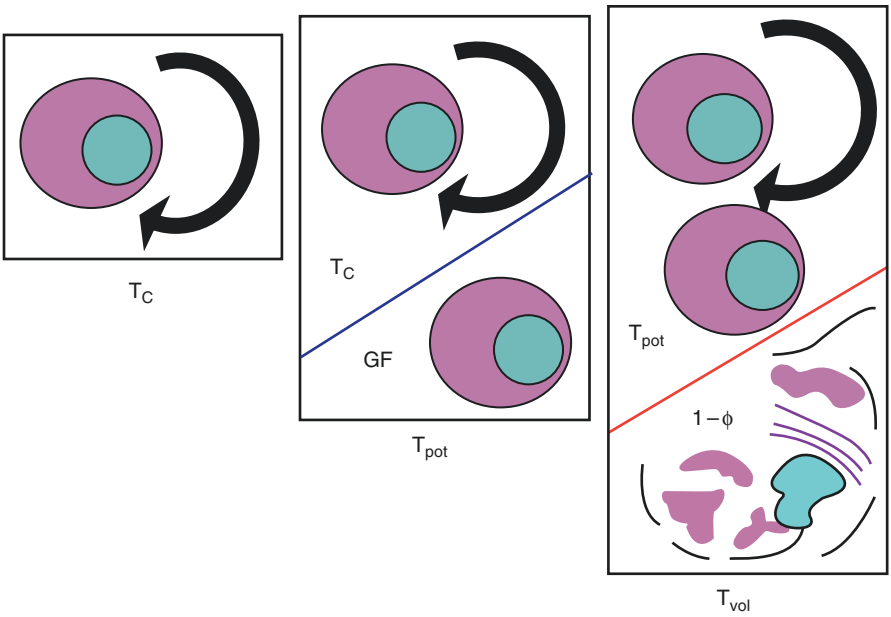

Fig. 27.4 The time it takes for a cell to move from G1 through mitosis is the cell cycle time (T_C). Cell cycle time (T_C) divided by the growth fraction (GF) is the potential doubling time (T_{pot}). The potential doubling time (T_{pot}) divided by the cell loss time is the volumetric doubling time (T_{vol}). See Eq. 27.3

Classic example: squamous cell CA.
A tumor with slow $\mathbf{T_{pot}}$ and small $\boldsymbol{\phi}$ grows slowly and responds slowly (if at all).
Classic example: sarcoma.

Growth Kinetics of Clinical Tumors

- An "average" human tumor has a cell cycle time ($\mathbf{T_C}$) of 2d and a potential doubling time ($\mathbf{T_{pot}}$) of 5d.
- With a cell loss factor ($\boldsymbol{\phi}$) of 75% this gives:
  - Volume doubling time ($\mathbf{T_{vol}}$) = **20d**.
  - Diameter doubling time ($\mathbf{T_d}$) = **60d**.
- Of course, these numbers vary a lot from patient to patient, or even for two metastases in the same patient.
  - As tumors grow, they may become more necrotic. This increases $\boldsymbol{\phi}$ and slows down $\mathbf{T_{vol}}$ and $\mathbf{T_d}$.
- **Accelerated repopulation** is a phenomenon in which prolonged cytotoxic treatment stimulates tumor cells to rapidly divide.

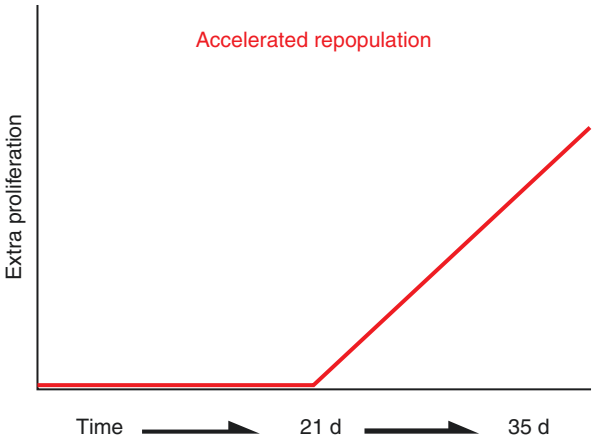

Fig. 27.5 Once treatment has started, some tumors may undergo accelerated repopulation that begins at a "kickoff time"

  - This is a well-known phenomenon in squamous cell cancers of the head and neck, and uterine cervix (Fig. 27.5).
- **Accelerated repopulation** is characterized by these parameters:
  - "**Kickoff time**" ($\mathbf{T_k}$): ~21–28 days delay from the start of treatment to the start of accelerated repopulation.
  - $\mathbf{T_{pot}}$: once accelerated repopulation starts, $\mathbf{T_d}$ approximates $\mathbf{T_{pot}}$. This is much faster than the usual $\mathbf{T_{vol}}$.

Accelerated Repopulation and Effective Dose

- For overall treatment times that exceed $\mathbf{T_k}$, **extra dose** must be given to counteract accelerated repopulation.
- The daily dose required to counteract accelerated repopulation is known as $\mathbf{D_{prolif}}$.
  - For H&N, lung, and CNS tumor cells, this number varies from **0.4** to **0.8** Gy/day.
  - See Chap. 23 for details.
- During a prolonged treatment time, accelerated repopulation increases the survival of both tumor cells and proliferating normal tissues such as skin and mucosa.
  - However, nonproliferating normal tissues cannot repopulate.
  - Giving extra dose for prolonged treatment time comes at a risk of increased late toxicity.
  - This is one reason why split course therapy (intentional treatment breaks) has fallen out of favor.

Cell Cycle Synchronization

- **Why use synchronized cells?**
  - In order to measure cell cycle dependent effects.
- **Mitotic harvest (shakeoff):**

  - Cells are grown as an adherent monolayer on the surface of a container.
  - Mitotic cells temporarily lose their adherence and can be physically dislodged and used in experiments.
- **Hydroxyurea (HU):**
  - **HU** selectively kills S-phase cells.
  - If cells are incubated in **HU**, they accumulate at the **G_1-S** checkpoint.
- **Other drugs:**
  - Any drug with selective killing or blocking of a specific phase of the cell cycle may be used to synchronize cells.

Cell Cycle and Radiosensitivity

- **Overall sensitivity (D_0):**
  - Cells are **most sensitive** to RT in **G_2/M**.
    A cell in **G_2/M** does not have enough time to repair DNA damage before dividing.
    DNA damage leads directly to mitotic catastrophe.
  - Cells become gradually **less sensitive** in **G_1** to **early S** and are **least sensitive** to RT in **late S**.
- Homologous recombination repair is most active during late-S phase, after most of the DNA has been replicated.
- **Shoulder Size (D_q):**
  - There is practically **no shoulder** to the survival curve in **G_2/M**, suggesting that very little repair takes place.
  - There is a moderate shoulder in **G1** to **early S**.
  - There is a very large shoulder in **late S** (Fig. 27.6).
- **Oxygen dependence (OER):**
  - **OER** is highest in S phase due to **increased DNA repair** under hypoxic conditions.
    Remember, oxygen makes DNA damage more difficult to repair.

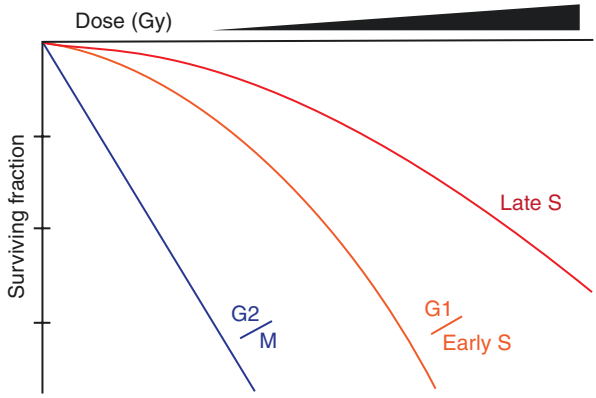

Fig. 27.6 Dose–response curves for cells from the various phases of the cell cycle typically demonstrate that G2/M phase cells are more radiosensitive, while late S -phase cells are more radioresistant

  - This causes the **OER** fraction size effect:
    Small fractions: Killing is dominated by the most sensitive cells (**G_2/M**) with the **lowest OER**.
    Large fractions: Survival is dominated by the least sensitive cells (**late S**) with the **highest OER**.
- **High LET Radiation:**
  - Cell cycle dependence still exists for high-LET radiation, but it is greatly decreased.

Fractionated RT and Reassortment

- **S** phase cells are radioresistant. It takes very high doses to kill them in a single fraction.
- With fractionated radiation, tumor cells can **reassort** in between fractions.
  - **Reassortment** of radioresistant S-phase cells into more radiation sensitive phases/parts of the cell cycle **improves** the therapeutic ratio of fractionated radiotherapy.
- In certain low-dose-rate (**LDR**) scenarios, cells can progress through the cell cycle and accumulate at the radiosensitive **G_2** phase.
  - This greatly increases radiosensitivity and is known as the **inverse dose-rate effect** (cell survival decreases with lower dose rates instead of increasing).
  - See Chap. 32 for details on low-dose-rate therapy.

Acute Effects of Total Body Irradiation (TBI)

28

Introduction

Total body irradiation (TBI) effects depend on the dose and the time that elapses between the irradiation and when one observes the effects in various organ and tissue systems which in turn depends on the life of the functional cells and differences in stem cell population kinetics. After acute TBI doses of 1 Gy or more, individuals may experience a prodromal reaction involving fatigue, anorexia, and vomiting. At doses of 2.5 Gy or more, individuals experience symptoms or die from the hematopoietic syndrome 30–60 days after exposure. At doses of 10 Gy or more, individuals will manifest symptoms of the gastrointestinal (GI) syndrome, causing death within 3–10 days. At very high doses, the cerebrovascular syndrome results in death within 24–48 h. Individuals exposed to doses likely to result in the hematopoietic syndrome can sometimes be rescued through supportive care, administration of cytokines and hematopoietic growth factors, and bone marrow transplants. There are various methods to estimate total body exposure.

Where Do the Data Come From?

Most data on the effects of acute whole-body radiation exposure come from experiences with humans and animal models. Because there has been so much data accumulated by studying effects on humans, we know that exposure to large doses does not turn people into hulking green superheroes, nor does it cause people to grow or shrink to ridiculous sizes as inferred by several 1950's Sci-Fi movies!

- **Human data:**
  - **Atomic bomb survivors and victims of the Chernobyl disaster or other criticality accidents**.

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Hundreds of thousands of exposures in Japan, but dose assessment was often inaccurate or unknown.

Note: No deaths or cases of the acute radiation syndromes (ARS) were noted as a result of the Fukushima Daiichi disaster in 2011.

  - Depending on the literature being cited, there have been ~400 deaths attributed to acute high dose exposures from sealed source, reactor, or criticality accidents.

    Patients that survived were more likely to have received prompt medical care after receiving doses less than 10 Gy.
- The **acute radiation syndrome** may be elicited by very high dose rate exposures such as from nuclear bombs and criticality accidents but may also be elicited after **intentional TBI**, which is administered at very low dose rates (5–10 cGy/min) and may result in a different toxicity profile.
  - The clinical data shows a significant dose-rate dependence for pulmonary toxicity (radiation pneumonitis).
- **Animal data:**
  - Dogs and non-human primates have similar radiosensitivity to humans.
  - Smaller animals such as mice are generally more radioresistant. This is thought to be due to increased hematopoietic stem cell densities in the bone marrow.

Prodromal Radiation Syndrome

- Characterized by **neuromuscular** and **gastrointestinal** symptoms.
- Occurs after a dose of ≥1 Gy, but severity is dose-related.
- Depending on dose, may occur soon after an acute exposure and can last for several days. Duration is also dose-related.
- Dose expected to be lethal in 50% of test subjects ($\mathbf{LD_{50/60}}$):
  - **~3–4 Gy** without medical intervention (best estimate usually cited as 3.25 Gy).
  - Symptoms include fatigability, anorexia, nausea/vomiting.
- At near-**supralethal and supralethal doses** (**8–10 Gy**):
  - Symptoms include diarrhea (immediate diarrhea if supralethal), fever, hypotension.
  - If doses are known to be supralethal, these patients should be provided with palliative care only.
  - Bone marrow transplants may be helpful for exposures between 8 and 10 Gy.

Cerebrovascular Syndrome

- Occurs after a dose of **~100 Gy**.
- Death is inevitable and occurs within **24–48 h after exposure**.

- Characterized by disorientation, incoordination, shortness of breath, hypotension, loss of consciousness, seizures, and death.
- Believed to be caused by increased intracranial pressure due to permeability of cerebral blood vessels.

Gastrointestinal Syndrome

- Occurs after a dose of **≥10 Gy**.
- Death usually occurs within **3–10 days**.
  - This timeframe is equal to the lifespan of intestinal epithelial cells.
- Characterized by nausea, vomiting, and prolonged diarrhea, followed by sepsis and death due to GI infection.
- Secondary to **loss of villi** throughout the GI tract, with resultant permeability and gut bacteria translocation.
- Due to a lack of mitigators for the GI syndrome, death is currently inevitable.

Hematopoietic Syndrome

- Occurs after a dose of **≥2.5 Gy**.
- Likely to be lethal at doses **≥4 Gy without intervention**.
- Death occurs within **30–60 days**.
  - This timeframe is similar to the lifespan of neutrophils and platelets.
- Lethal dose is expressed as $\mathbf{LD_{50/60}}$, the 50% lethal dose at 60 days.
- Characterized by a **latent period** in between the prodromal syndrome (few days) and symptomatic cytopenias (few weeks).
  - There may not always be a clearly defined latent period; symptoms can merge gradually from prodromal to hematopoietic.
- **Symptomatic period**: fatigue, anemia, hemorrhage, fever/chills, mouth ulcers, epilation.
  - Symptoms are due to pancytopenia.
  - Death occurs mostly due to infection (neutropenia, leukopenia).
- May be treated with supportive care (antibiotics, growth factors) or stem cell transplant.

Cutaneous Radiation Injury (CRI)

- Observation of skin injury may occur when symptoms of other syndromes are manifested, but some symptoms of CRI could appear within hours or weeks after exposure and are dose-dependent. A dose of ≥2 Gy is usually sufficient to induce Grade 1 injury; one might observe a prodromal response early (e.g., in 2 days) or a latent period of 5 weeks or so, after which some slight edema and pigmentation

might occur. Dry desquamation might occur a few months later. Slight skin atrophy or skin cancer may occur as late effects. After higher doses, one might observe edema, epilation, and erythema early, giving rise to wet or dry desquamation, ulceration, and necrosis later.

The LD_{50} and Dose-Time Response

- The **$LD_{50/60}$** for humans is approximately **3–4 Gy** without medical intervention and **up to ~ 8 Gy** with standard medical care.
  - The **LD_{50}** may or may not be increased by stem cell transplantation.
  - While a dirty bomb is unlikely to result in many or any acute exposures that are close to or that exceed the **LD_{50}**, the **LD_{50}** is likely to be closer to the oft-cited "best estimate" of 3.25 Gy for victims of nuclear terrorism involving an improvised nuclear device or warfare, as timely treatment of mass casualties will be difficult, and individuals will have combined radiation injury and trauma or burns.
- **Cytopenias and time courses**:
  - Radiation kills off hematopoietic stem cells; most mature functional cells are relatively resistant.
    Exception: lymphocytes which undergo apoptosis.
  - Cytopenias occur as functional cells die and cannot be replaced due to loss of upstream progenitor stem cells.
    Therefore, the time course of cytopenia is dependent on the lifespan of the mature cell.
  - **Lymphocytes** begin to drop immediately.
  - **Granulocytes** begin to drop within days.
  - **Platelets** drop after a few weeks.
  - **Erythrocyte** (RBC) lineage is relatively radioresistant, and anemia usually does not occur from erythrocyte lineage suppression.
  - WBC and platelet nadir typically occurs around 3–4 weeks, although this may be dose-dependent.
  - If complete neutropenia occurs within <3 days, it indicates a supralethal dose.

Dose Estimation in Radiation Disasters

- **Symptoms**:
  - Immediate diarrhea, fever, or hypotension indicates a massive, unsurvivable dose.
  - Lack of vomiting within a few hours after exposure indicates a sub-lethal dose.
  - Victims with nausea as their initial symptom are most likely to have received a potentially lethal but potentially survivable dose.
- **Time course**:
  - Very rapid drop in blood cell counts (nadir <3 days) indicates supralethal dose.
  - Gradual drop in counts (nadir ~3 weeks) indicates potentially survivable dose.

- **Peripheral blood lymphocytes as a biodosimeter**:
  - Peripheral blood lymphocytes are extracted from exposed individuals and subjected to mitogens in vitro.
  - During mitosis, these cells may display asymmetrical exchange-type chromosomal aberrations such as rings and dicentrics.
    Counting the aberrations per cell from exposed individuals can provide an accurate estimate of total-body radiation doses over **~0.25 Gy when compared to a standard curve**.
  - **Stable aberrations**, such as translocations, persist for the remainder of that individual's lifetime.
  - **Unstable aberrations**, such as rings and dicentrics, decline over time as the affected cells die.

Supportive Care

- Isolation and antibiotics are the most important component of supportive care.
  - Patients receiving near-lethal doses will be profoundly immunosuppressed for several weeks.
  - Contact (barrier) isolation is vital.
  - Neutropenic precautions, avoid soil organisms.
- Give platelets when platelets drop.
- Give PRBCs if bleeding occurs.

Radioprotectors, Countermeasures, Chelators, and Stem Cell Transplants

Amifostine

- Has been shown to increase the $\mathbf{LD_{50}}$ in animals and known to protect some normal tissues in humans receiving radiotherapy treatments, but must be administered prior to irradiation to have a protective effect, and so it is NOT considered to be a radiation countermeasure for mass-casualty events such as nuclear accidents or terrorism. Causes severe nausea and vomiting at the doses required for radioprotection.

Cytokines and Hematopoietic Growth Factors

- **Granulocyte colony-stimulating factor (G-CSF)** is an effective stimulator of hematopoiesis and shortens neutrophil recovery time after radiation exposure. However, daily injections are required and should be started within 72 hours after exposure.
- **Filgrastim** (trade name: Neupogen) is a synthetic analog of human G-CSF that received approval from the FDA for treatment of acute radiation injury.

- **Pegfilgrastim** (trade name: Neulasta) is filgrastim with polyethylene glycol added and only needs to be administered once per week. Also FDA-approved for use in treating mass casualties, but first was shown to reduce infection risk due to low WBC counts experienced during chemotherapy.
- **Sargramostim** (trade name: Leukine) is human recombinant **granulocyte-macrophage colony-stimulating factor (GM-CSF)**; it is yet another agent that has received FDA approval for the treatment of symptoms of the hematopoietic acute radiation syndrome (it can hasten recovery after myelosuppression).

Chelators

- Used to reduce internal contamination by several heavy metal radioactive elements released by dirty bombs, power plant accidents, or nuclear detonations.
- **Ca-DPTA or Zn-DTPA** are used to chelate Pt, Am, Cm (stabilized complexes are excreted in urine).
- **Prussian blue** chelates Cs and Tl in intestines, preventing reabsorption by the body. The compound enhances fecal excretion of these radioisotopes.

Stem Cell Rescue

- **Allogeneic stem cell transplants** are used to treat various malignancies and hematologic conditions.
  - Myeloablative (full-intensity) protocols often include **TBI** as part of the conditioning regimen.
  - Fractionated TBI may be given at a dose of 11–13 Gy delivered BID or TID for 4 days.
  - Partial transmission lung blocks may be used to decrease pulmonary toxicity.
  - Stem cell transplantation is performed within days after TBI. Patients then require intensive medical care for many weeks.
- Bone marrow (stem cell) rescue has been attempted for some nuclear accident survivors, but it is uncertain how much benefit it gives in the accidental setting.
  - Highly unlikely to have a good HLA match in a nuclear disaster setting.
  - Narrow dose window of utility.

    <8 Gy: patients may be able to survive with standard medical care, such as antibiotics, transfusions, and growth factor support.

    >10 Gy: patients are likely to die even if transplanted.

    GI syndrome is likely to occur, and donor cells may fail to engraft due to damage to bone marrow stroma.

Other Notes Regarding Treatment of Mass Casualties

- Critical injuries or conditions should be treated first. Things such as preventing contamination, decontamination, treatment of minor injuries, or treatment for internal contamination should occur only after life-threatening conditions are addressed.
- It is extremely unlikely that victims would be so heavily contaminated that they would pose a radiation risk to healthcare workers.
- Potassium iodide would only be recommended for individuals exposed to radioactive iodine in milk and food immediately or later after exposure.
- For CRI, one can use anti-itch medications and antihistamines, as well as anti-inflammatories and other soothing topical creams. During the latent stages of CRI, antibiotics (to reduce risk of infection) and proteolysis inhibitors may be helpful.

Time Dose and Fractionation Effects

29

Introduction

The linear-quadratic (LQ) model utilizes the terms α (single-hit kill) and β (two-hit kill) which correlate with low-dose killing and high-dose killing, respectively. Fractionation experiments with normal tissues (Chap. 23) for survival and functional tissue endpoints and tumor survival have allowed calculation of α/β ratios. These α/β ratios along with dose per fraction and total dose can be used to calculate biologically equivalent doses (BEDs) based on fraction size and total dose for various tissues and tumors compared to standard single fractions of no more than 2 Gy once a day, 5 days per week.

Fractionation Definitions

- **Standard Fractionation**: Once daily, 5 days/week, no more than 2 Gy/fraction
  - **Split Course**: RT with planned treatment breaks
- **Altered Fractionation**: Anything other than standard fractionation
- **Accelerated Fractionation**: Any fractionation schedule that gives >10 Gy/week. Subtypes include the following:
  - Pure accelerated fractionation (2 Gy/fx, 6–7 fx/week)
  - Accelerated hypofractionation (>3 Gy/fx)
  - Accelerated hyperfractionation (>1 fx/day)
- **Hypofractionation**: Increased fraction size, with or without decreased number of fractions/week
  - **Stereotactic Radiation (SRS/SBRT/SABR)**: RT delivered with stereotactic localization techniques in five fractions or less
  - **Fractionated Stereotactic RT (FSRT)**: RT delivered with stereotactic techniques and more than five fractions
- **Hyperfractionation**: Decreased fraction size with more than one fraction per day (BID or TID)

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- **Concomitant Boost (CB)**: Two fractions per day with one fraction to a large field and the other to a boost volume
- **Simultaneous Integrated Boost (SIB)**: One fraction per day with a higher dose to a boost volume and a lower dose to the large field

Linear-Quadratic (LQ, Alpha-Beta) Model

- The **Linear-Quadratic Model** was developed after the in vitro observation that DNA damage follows a linear-quadratic relationship with dose (see Fig. 29.1).
- **Lethal DNA aberrations = $\alpha D + \beta D^2$ = Cell Kill**

$$SF_D = e^{-\left(\alpha D + \beta D^2\right)} \tag{29.1}$$

- Unlike the single-hit model, the **LQ Model** accounts for two different types of lethal hits which are based on known molecular mechanisms of DNA damage:
  - **Single-hit kill (α)** is unrepairable damage and is independent of fractionation or dose rate.
    This corresponds to single-hit and intra-track accumulated damage (see Chap. 21).
- **Two-hit kill (β)** is repairable damage and depends on fractionation and dose rate. This corresponds to inter-track accumulated damage (see Chap. 21).
- The **α/β ratio** is the dose at which **α** kill and **β** kill are equal.
  - **Low α/β ratio** ("high repair") tissues are relatively resistant at a small fraction size and relatively sensitive at a large fraction size.
  - **High α/β ratio** ("low repair") tissues are relatively sensitive at a small fraction size and relatively resistant at a large fraction size.

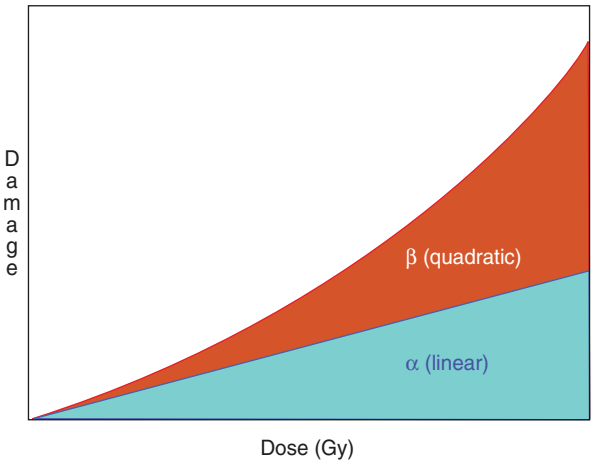

Fig. 29.1 The linear-quadratic DNA damage curve. Total DNA damage can be expressed as the sum of "linear" damage (not fraction size-dependent) and "quadratic" (fraction size-dependent) damage. Figure repeated from Chaps. 21 and 23

Alpha-Beta Ratios of Tissues and Tumor

- Most acute-reacting tissues are believed to have an α/β ratio ≈ 10.
- Most late-reacting tissues are believed to have an α/β ratio ≈ 3 or less.
- CNS tissue (brain, cord) is believed to have an α/β ratio ≈ 1–2.
- Most tumors are believed to have an α/β ratio ≥ 10.
- Some low α/β tumors may have an α/β ratio ≈ 1.5–4.
  - Breast and Prostate are the "classic" low α/β tumors.

Alpha-Beta Model and Dose Fractionation

- Based on the **LQ** model, the rationale for dose fractionation is that tumors have a higher **α/β** ratio than normal tissues (see Fig. 29.2).
- By using smaller fraction sizes, the normal tissues with a low **α/β** are relatively spared.
- Late-reacting tissues, such as CNS, are especially sensitive to fraction size due to their low **α/β** ratio.
- Tumors with a low **α/β** ratio may not benefit as much from fractionation.

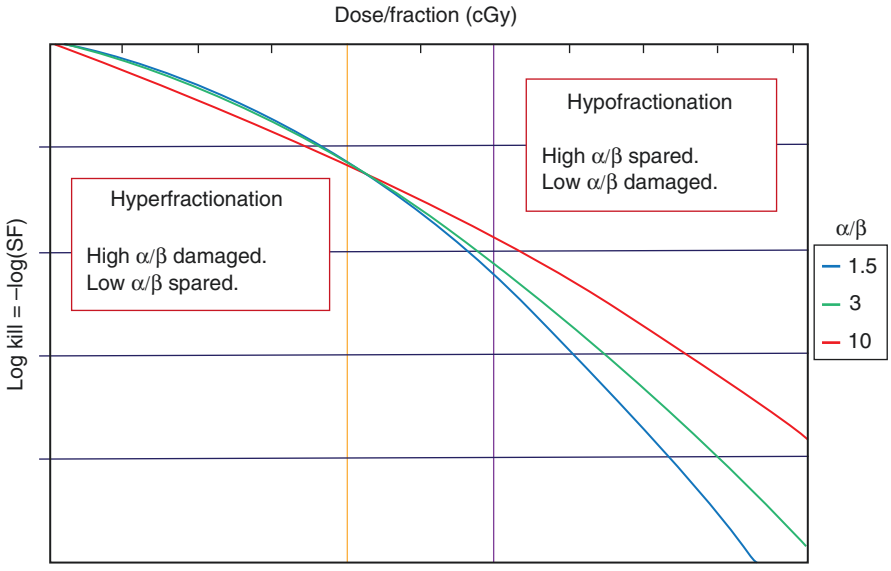

Fig. 29.2 Fraction size and relative kill. Small fraction sizes are relatively more effective at killing high α/β tissues. Large fraction sizes are relatively more effective at killing low α/β tissues

Alpha-Beta Model: Biologically Effective Dose

- One advantage of the linear-quadratic model is that it is easy to calculate effective doses for different fraction sizes.
  - This makes it very useful in clinical practice.
- **Biologically effective dose (BED)** is an extrapolated dose given over infinitely many fractions.
  - This is the opposite of Nominal Standard Dose (NSD), shown later in this chapter, which is an equivalent single-fraction dose.
- For ***n*** fractions of ***d*** dose per fraction:

$$\mathrm{BED}_{\alpha/\beta} = n \times d \times \left(1 + \frac{d}{\alpha/\beta}\right) \tag{29.2}$$

- Note that **BED** is *always* greater than physical dose (**nd**).
- **Example Question (1)**:
  - You want to limit the spinal cord ($\alpha/\beta = 2$) to no more than 98 Gy BED_2. What constraint should you use for treating the spine with 3 Gy daily fractions?
    Each 3 Gy fxn: **BED_2 (3 Gy)** = 3 * 2.5 = **7.5 Gy_2**.
    98 Gy_2/7.5 = **13.07** fractions.
    13 × 3 Gy = **39 Gy** maximum dose.
- A closely related number is the **equivalent dose in 2 Gy fractions ($EQD_{\alpha/\beta,2}$)**.

$$\mathrm{EQD}_{\alpha/\beta,2} = n \times d \times \left(\frac{\alpha/\beta + d}{\alpha/\beta + 2}\right) \tag{29.3}$$

  - This number can be used to sum up partial treatment courses given at different fraction sizes.

- **Example Question (2)**:
  - You want to treat a lung cancer to 60 Gy in 2 Gy fractions, but the first five fractions are given at 3 Gy/fx due to SVC syndrome.
  - Assuming $\alpha/\beta = 3$, how much additional dose should you deliver at 2 Gy per fraction?
    3 Gy × 5: $EQD_{3,2}$ = 15 * 6/5 = 18 Gy equivalent.
    60–18 Gy = 42 Gy remaining.
    So you would give an additional 42 Gy @ 2 Gy/fxn.

Alpha-Beta Model: Correction Factors

- The **Thames H-factor** is an incomplete repair correction factor that is applied to regimens delivered twice or three times daily. It varies roughly from 0 to 1.
  - For alpha-beta calculations, dose per fraction is multiplied by (**$1 + H_m$**), where **m** is the number of fractions per day.

  - **Example**: You are treating a lung with 45 Gy @ 1.5 Gy BID, spaced 6 h apart. Assuming that $H_2 = 0.2$, what is the equivalent dose @ 1.8 Gy/day?
    Effective fraction size = 1.5 Gy × 1.2 = 1.8 Gy.
    So this is equivalent to 45 Gy @ 1.8 Gy daily.
- The **g-factor** is a number used to convert continuous irradiation (such as LDR brachytherapy) into an equivalent daily fraction size.
- The **accelerated repopulation correction factor ($\mathbf{D_{prolif}}$)** corrects for proliferation during a prolonged treatment time (see Chap. 27 for details on accelerated repopulation).
  - After a "kickoff time" $\mathbf{T_k}$, tumor cells begin proliferating much faster than normal.
  - For an overall treatment time $\mathbf{T > T_k}$:
  - **Corrected $\mathbf{EQD_2} = \mathbf{EQD_2} - ((T - Tk) * D_{prolif})$.**
  - So if $D_{prolif} = 0.7$ Gy/day, you lose 0.7 Gy of effective dose for each day of accelerated repopulation.

Ellis Nominal Standard Dose (NSD)

- An empiric equation based on the **Strandquist Plots**:
  - Back in the 1930s–1940s, Strandquist treated a bunch of skin cancers and plotted radium exposure versus skin erythema, desquamation, necrosis, and tumor cure.
  - He found that the relationship between total dose and overall treatment time formed a series of parallel lines on a logarithmic chart.
  - This predates the linear-quadratic model by many decades (see Fig. 29.3).
- Unlike newer models, the Ellis NSD has no theoretical basis whatsoever; it is an empiric "curve fitting" model.
- The NSD can accurately predict acute skin toxicity and skin cancer response because that is where the data came from.

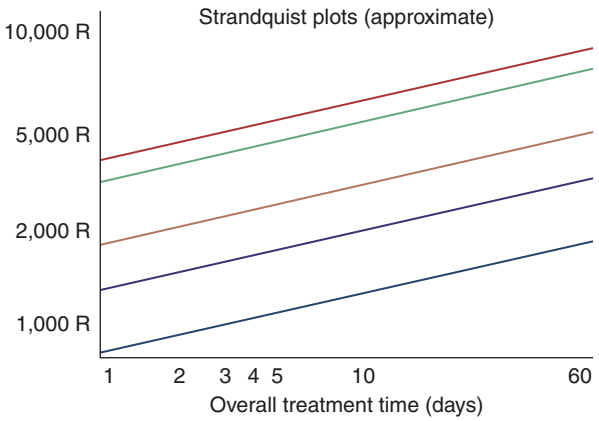

Fig. 29.3 The Strandquist plots (approximate). These parallel lines represent various skin-related endpoints such as erythema, desquamation, and necrosis

  - The NSD makes no attempt to predict late toxicity.
- There are two versions of the equation: one with time and fractionation, another with just fractionation.
- For N fractions delivered over T days:

$$\mathrm{NSD} = N^{0.24} \times T^{0.11} \tag{29.4}$$

or

$$\mathrm{NSD} = N^{0.33} \ \left(\text{ignoring time}\right) \tag{29.5}$$

$$\mathrm{NSD}\ \left(rets\right) = \frac{\text{Dose}\ \left(Gy\right)}{\text{NSD Factor}} \tag{29.6}$$

Very Large Fractions: SBRT/SRS

- The **LQ** model of cell killing does not appear to be accurate for very large fractions.
  - **LQ** predicts extremely high quadratic killing, but this does not correlate with experimental observations.
  - At very large fraction sizes, there may be additional mechanisms for cell killing and cell survival.
  - At very large fraction sizes, cell survival may be dominated by a small population of radioresistant cells.
- Many different models exist for predicting cell kill at very large fraction sizes.

Other Radiation Survival Models

- The **single-hit**, **LQ**, and **NSD** models are popular because they are simple enough to calculate by hand.
- More complicated mathematical models exist and are briefly mentioned below.
- **Two-Component Model**
  - Combines a single-hit single-target ($\mathbf{D_1}$) and a single-hit multitarget model ($\mathbf{D_0}$, $\mathbf{D_q}$).
  - Behaves fairly similar to **LQ** model, except the survival curve stops bending at very high doses.
- **Universal Survival Curve (USC)/Single-Fraction Equivalent Dose (SFED)**
  - Combines an **LQ** and **single-hit** ($\mathbf{D_0}$) curve so that the survival curve stops bending at very high doses.
  - Used for calculating **SRS/SBRT** doses.
- **Lethal–Potentially Lethal (LPL) Model**
  - Damage is classified as lethal or potentially lethal.

  - Potentially lethal damage is either repaired over time or mis-repaired into lethal damage.
  - Multiple potentially lethal hits can become lethal.
  - Shape of curve is extremely similar to **LQ** model, but **LPL** can more accurately model dose rate and fractionation factors.
- **Repair Saturation Model**
  - Initial damage follows a straight-line exponential function but is repaired into a survival curve with a shoulder.
  - At high doses, repair becomes saturated and is unable to keep up with damage induced, which is assumed to be linear.
  - Shape of curve is very similar to **single-hit** curve.
- **Induced Repair Model**
  - Used to explain hyper-radiosensitivity at a very low dose per fraction.
  - Follows a radiosensitive **LQ** curve at a low dose and a radioresistant **LQ** curve at a high dose.

Therapeutic Ratio

30

Introduction

The objective of radiation therapy is to control tumors without causing excessive normal tissue toxicity. Predictive models may be used to compute tumor control probabilities (TCP) as well as normal tissue complication probability (NTCP). Increasing the dose or volume of radiation tends to increase both values. The difference between TCP and NTCP is called the therapeutic window. Factors such as geographic miss and accelerated repopulation can decrease TCP and thus decrease the therapeutic window. The therapeutic window may be modified by combining radiation therapy with other modalities such as chemotherapy and immunotherapy.

Tumor Control Probability (TCP) Curves

- A **TCP curve** is created by plotting some measure of tumor control probability against the total dose.
- This may be done with clinical or experimental data, or with theoretical models.
- Even when plotting clinical data, a theoretical model must be used to model the response of tumor cells to radiation therapy.
  - See Chap. 23 for details of single-target and linear-quadratic models.
- A **TCP** curve is characterized by a sigmoid shape, in which there is little dose–response at very low or very high doses, and a steep dose–response at intermediate doses.

Calculation of TCP

- Assuming that a single clonogenic cell is capable of reproducing an entire tumor, the probability of tumor control is equal to the probability that no clonogenic tumor cells are present.

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- Using simple Poisson statistics (see Chap. 23), if there are an average of **X** clonogenic tumor cells present, tumor control probability is equal to $\mathbf{e}^{-X}$.
- **Rule of Thumb**: To achieve a certain **TCP**, you should aim for a tumor cell survival of (**1 – TCP**).
  - So to achieve **90% TCP**, you need a tumor cell survival of **0.1 tumor cells per patient**.
  - This means that if you start out with $\mathbf{10^9}$ tumor cells, you need to achieve a **surviving fraction** of $\mathbf{10^{-10}}$.

Factors Affecting Shape and Slope of TCP Curves

- The slope of a tumor control probability curve is known as **γ**.
  - **γ** is a ratio of **absolute** change in response probability to **relative** change in dose.

$$\gamma = \frac{\Delta\text{Response}\ (\text{absolute}\%)}{\Delta\text{Dose}\ (\text{relative}\%)} \tag{30.1}$$

  - At **γ = 2**, a 1% increase in dose will increase **TCP** by 2%.
  - As demonstrated in this graph, γ is highest near the middle of the **TCP** curve (Fig. 30.1).
  - There is a shallow dose–response (low γ) at very low and very high doses, and a much steeper dose–response at intermediate doses.

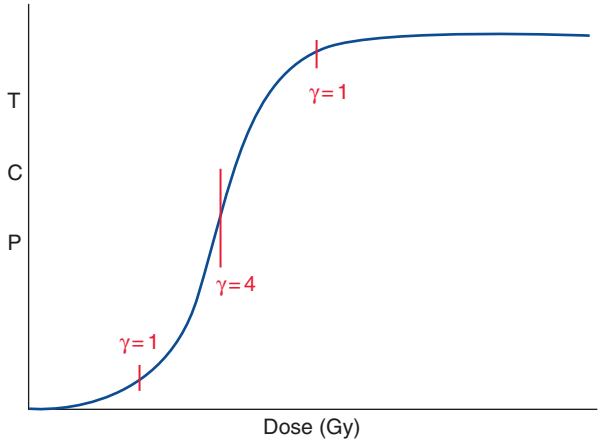

Fig. 30.1 TCP curve showing various γ values

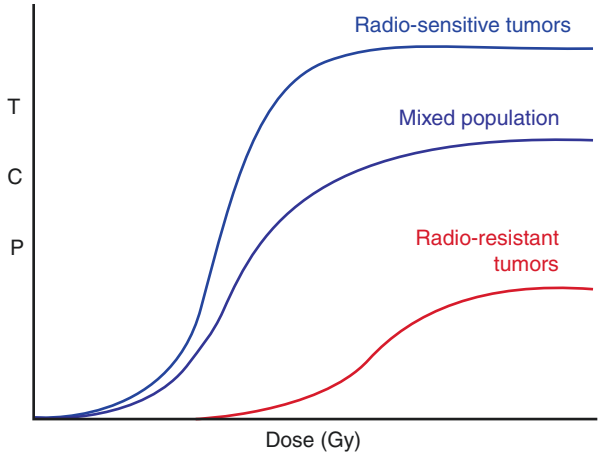

Fig. 30.2 TCP curve showing a mixture of sensitive and resistant tumors

- The slope of a **TCP** curve depends on how the dose is given:
  - If dose escalation is performed by adding more fractions at a fixed fraction size, the measured **γ** will be lower than if dose escalation is done by increasing fraction size (Fig. 30.2).
- A mixed population of tumors will always show a weaker dose–response than a homogeneous population.
  - Very sensitive tumors are controlled even at the lowest dose levels, and very resistant tumors are uncontrolled even at the highest dose levels.
- Geographic miss becomes even more important at very high levels of **TCP**:
  - Patients with viable tumor outside of the radiation field will fail no matter how high the dose is escalated.

Normal Tissue Complication Probability (NTCP)

- An **NTCP** curve is constructed the same way as a **TCP** curve, by plotting the probability of normal tissue injury against the dose.
- Normal tissue tends to have a steeper dose–response than tumors.
- Different normal organs have different volume dependence as seen in Chap. 25.
  - The **LKB** model takes this into account with a volume exponent, *n*.
  - Tissues with a large volume effect (parallel tissues) have a larger *n*, while tissues with a small volume effect (serial tissues) have a smaller *n*.
- Normal organs are rarely homogeneously irradiated. Therefore, there must be a mechanism to account for different volumes of irradiation:
  - The **Lyman–Kutcher–Burman (LKB) model** takes a **dose–volume histogram (DVH)** and calculates an equivalent dose and volume assuming uniform irradiation to a partial organ.

- Take this type of analysis with a grain of salt; it is a mathematical approximation and does not have a strong biological basis.

Therapeutic Window and Therapeutic Ratio

- The "**therapeutic window**" is a figurative space in between treatment failure and toxicity.
  - This is a conceptual window and not a quantitative number.
  - The larger the window, the more likely the treatment is to be safe and effective (Fig. 30.3).
- **Therapeutic ratio** is the difference between tumor control and normal tissue toxicity.
  - One popular measure of **therapeutic ratio** is the **probability of uncomplicated cure**; as defined by (probability of cure)*(1 − probability of complication).
  - In other words,

$$\mathrm{TR} = \mathrm{TCP}! \times \left(1 - \mathrm{NTCP}\right) \tag{30.2}$$

  - Keep in mind that this is just one way to define **TR**.
- **Therapeutic ratio** depends greatly on the definition of "complication."
  - Most patients have some level of toxicity, especially for sites like H&N.
  - What level of toxicity is acceptable versus unacceptable?

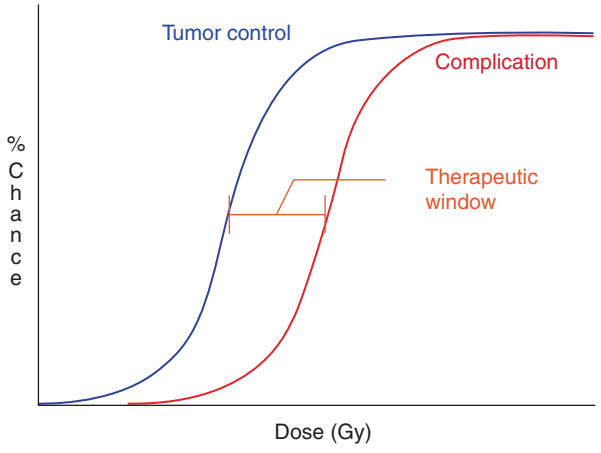

Fig. 30.3 The therapeutic window is the difference between the TCP curve and the NTCP curve

Tumor and Normal Tissue Repopulation

- When treatment is prolonged (as in split course radiation), both tumors and normal tissues can repopulate (Fig. 30.4).
- This increases the dose required to achieve the same **TCP** or **NTCP** and is visualized as a right shift of **TCP** and **NTCP** curves (Fig. 30.5).
  - In general, tumors repopulate more effectively than normal tissues.
  - Late-responding tissues do not repopulate effectively over clinically relevant timescales.
- In general, treatment prolongation narrows the therapeutic window and is a bad thing.
  - There is plenty of human data suggesting decreased survival with prolonged overall treatment time, especially in squamous cell cancers of the head and neck region or gynecologic regions.

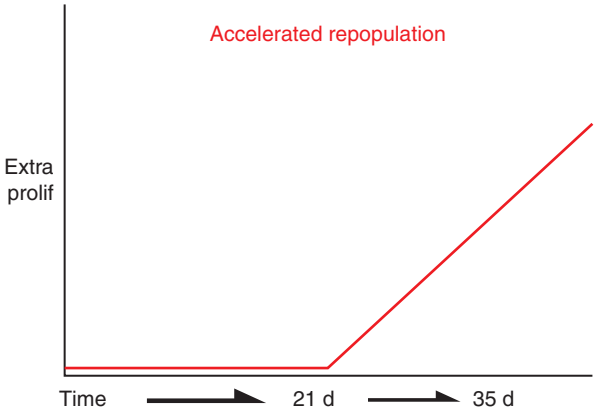

Fig. 30.4 Some tumors will undergo accelerated repopulation after a certain amount of time under treatment. This is called the kickoff time. This effect can often decrease the therapeutic window

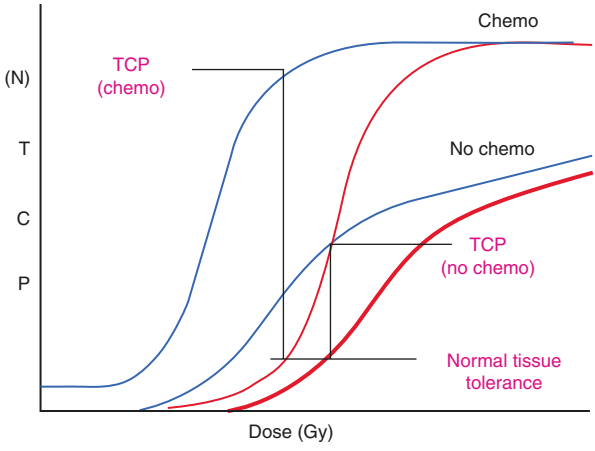

Fig. 30.5 TCP curves (*blue*) and NTCP curves (*red*) showing the effect of radiosensitizing chemotherapy (*left-shifted*) compared to no chemotherapy (*right-shifted*)

Sensitizers, Protectors, and Combined Modality

- The purpose of any combined modality therapy is to improve the therapeutic ratio.
- Mechanisms to improve therapeutic ratio include the following:
  - Selective sensitization of tumor
  - Selective protection of normal tissue
  - Independent (additive or synergistic) killing of tumor
  - Selective killing of radioresistant (i.e., hypoxic) tumor
  - Redistribution of tumor cells into radiation-sensitive phases of the cell cycle such as G2/M
  - Immunotherapy to reactivate the immune response to tumor and metastasis
- Combined modality therapy may or may not increase therapeutic ratio.
  - For example, concurrent cisplatin for head and neck irradiation increases both toxicity and cure rates. If your definition of therapeutic ratio places equal weight on toxicity and cure, it may not "improve" at all.
- See Chap. 31 for more details.

Chemotherapy, Chemomodulation, and Immunomodulation of Radiation Therapy

31

Introduction

Radiation therapy can be modified by increasing the effectiveness of radiation on tumors (radiosensitizers), protecting normal tissues (radioprotectors), increasing oxygen concentration, or by using systemic therapy drugs. Radioprotectors are described by their dose reduction factor (DRF) while radiosensitizers are described by their enhancement ratio (ER). Both numbers are a ratio of radiation doses required to achieve a biological effect. Systemic agents can be classified as hypoxic radiosensitizers, hypoxic cytotoxins, classic alkylators, platinum agents, antibiotics, antimetabolites, vinca alkaloids, taxanes, topoisomerase inhibitors, hormonal agents, monoclonal antibodies, small molecule inhibitors (usually tyrosine kinase inhibitors), and immunomodulators. Progress is also being made in the field of gene therapy, although this is not yet mainstream.

Radiosensitizers

- Unlike chemotherapy, these drugs have little to no tumoricidal effect unless given in combination with radiation.
- **Halogenated Pyrimidines**
  - **Bromodeoxyuridine (BUdR)** and **iododeoxyuridine (IUdR)**
- **Nucleotide analogues that are taken up and incorporated into newly synthesized DNA**.
  - **Only cells with active DNA synthesis will incorporate these analogues.**
  - **DNA containing nucleotide analogues is more susceptible to strand breakage from ionizing radiation, therefore tumor is selectively radiosensitized.**

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Radioprotectors

- These drugs are designed to selectively protect normal tissues from radiation damage.
- **Sulfhydryls (including WR-series aminothiol compounds and derivatives).**
  - Powerful free radical scavengers, developed during/after Cold War in anticipation of nuclear war/terrorism.
  - **Amifostine** is the only FDA-approved radioprotector.
  - Administered 30 min prior to RT, greatly decreases mucositis and xerostomia.
  - Normal tissue selectivity is based on the following:
    Slower penetration of tumors compared to well-vascularized normal tissues.
    Alkaline phosphatase required to activate amifostine. Many tumors are deficient in this enzyme.
  - Can cause nausea and hypotension and therefore is rarely used in modern clinical practice.

Oxygen-Modifying Therapy

- Hypoxia is a well-known determinant of radioresistance. Many strategies have been developed to cope with hypoxia.
- **Direct Oxygen Modification**:
  - **Transfusions**: RBCs, the oldest oxygen-modifying therapy. The clinical evidence for radiosensitization by transfusion is mixed.
  - **Hyperbaric Oxygen (HBO_2)**: Administered in a pressurized dive tank. Equipment and potential hazards make this option impractical for most medical centers.
  - **Carbogen**: A gas mixture of 95% O_2 and 5% CO_2, hyperoxygenates tissues like **HBO_2** but is easier to administer.
  - **Nicotinamide**: A vasodilator that decreases acute hypoxia.
  - **Accelerated radiation with carbogen and nicotinamide (ARCON)**: A clinically relevant treatment regimen developed in the Netherlands.
- **Hypoxic Radiosensitizers**:
  - These compounds increase the yield of DNA damage from irradiation under hypoxic conditions, much like oxygen itself.
  - **Nitroimidazoles** have a longer diffusion distance than oxygen and can therefore penetrate into a poorly vascularized tumor.
    These include **misonidazole, etanidazole, nimorazole,** and **pimonidazole**.
    Radiolabeled nitroimidazoles can be used to image hypoxic tumor cells.
  - Effective use as radiosensitizers is limited by cumulative neurotoxicity that develops at concentrations required during fractionated RT.
  - **Nimorazole** is clinically used as a radiosensitizer in Danish head-and-neck trials.

- **Hypoxic Cytotoxins**:
  - These compounds have inherent tumoricidal activity even in the absence of radiation.
  - **Mitomycin C** – chemotherapy drug, slightly more toxic to hypoxic cells. Very myelosuppressive, used routinely in anal cancer.
  - **Tirapazamine** – hypoxia-specific toxin that works very well in mice but is more toxic in humans. Used in ongoing clinical trials for hypoxic H&N tumors. Also sensitizes hypoxic cells to radiation.

Hypoxia Imaging

- The "Gold Standard" used for invasive hypoxia detection is **the oxygen probe**. Use of these probes is painful for patients.
- The noninvasive "gold standard" is hypoxia imaging with **O-15 PET** (radioactive oxygen).
  - **O-15** has a half-life of 2 min, so it has to be manufactured at or near the imaging site.
- **18F-MISO** and **62Cu-ATSM** are longer-lived positron emitters that accumulate in hypoxic cells and can be used for PET imaging.
- It is theorized that hypoxia-specific sensitizers and cytotoxins will be more effective when coupled with hypoxia imaging.
  - Select out a group of highly hypoxic tumors that will respond better to hypoxia-specific agents.
  - This is not yet proven by clinical data (as of 2013), but there are ongoing trials.

Dose Reduction Factor and Enhancement Factor

- Protectors are characterized by a **dose reduction factor (DRF)**, calculated as the **ratio of radiation doses** that achieve the same biological endpoint:

$$\mathrm{DRF} = \frac{\mathrm{Dose}\ (\mathrm{with\ protector})\ \mathrm{to\ achieve\ an\ effect}}{\mathrm{Dose}\ (\mathrm{no\ protector})\ \mathrm{for\ the\ same\ effect}} \tag{31.1}$$

  - Amifostine has a **DRF** of 1.8–2.7 for an endpoint of total-body irradiation lethality in mice.
- Sensitizers are characterized by an **enhancement ratio (ER)**, calculated as the ratio of doses that achieve the same biological endpoint:

$$\mathrm{ER} = \frac{\mathrm{Dose}\ (\mathrm{no\ sensitizer})\ \mathrm{to\ achieve\ an\ effect}}{\mathrm{Dose}\ (\mathrm{with\ sensitizer})\ \mathrm{for\ the\ same\ effect}} \tag{31.2}$$

  - **Misonidazole** has an **ER** as high as 1.8 for an endpoint of cell survival after single-fraction irradiation under hypoxic conditions.
- **Hypoxia-specific sensitizers** are never as effective in patients as one would expect from their **ER**. Why?
  - During a course of fractionated radiation, some portion of the tumor will undergo **reoxygenation**.
  - In the cells that successfully reoxygenate, real $\mathbf{O_2}$ is more effective than any drug.

Systemic Therapy Agents: Mechanism of Action

- **Classic Alkylators**: Kill cells by attaching alkyl groups to DNA.
  - Not usually cell cycle specific
  - May or may not be radiosensitizing
  - Penetrate blood–brain barrier
  - Include **cyclophosphamide, ifosfamide, temozolomide, busulfan, melphalan, dacarbazine, BCNU, CCNU**, et al.
- **Platinum**: Has both alkylating and cross-linking properties. Both can damage DNA.
  - Not cell cycle specific
  - Very radiosensitizing (careful – sometimes FX are additive)
  - Includes **cisplatin, carboplatin, oxaliplatin**, etc.
- **Antibiotics**: Kill cells by inhibiting DNA and RNA synthesis.
  - Not cell cycle specific
  - Very radiosensitizing—especially **adriamycin**
  - Include **doxorubicin, daunorubicin, actinomycin D, bleomycin, mitomycin C,** etc.
- **Antimetabolites**: Analogues of normal metabolites in cells. Kill cells by replacing normal metabolites with drug, inhibiting a variety of pathways.
  - S-phase specific (e.g., 5FU = DNA synthesis toxin)
  - Very radiosensitizing—especially **gemcitabine**
  - Include **methotrexate**, **5-FU**, **capecitabine**, **gemcitabine, cytarabine**, **hydroxyurea,** etc.
- **Vinca Alkaloids**: Derived from the *Vinca* periwinkle. Kill cells by blocking microtubule assembly.
  - M-phase specific (“spindle toxin”)
  - Do not cross blood–brain barrier, and are lethal if they get into the CSF
  - Include **vincristine, vinblastine, vindesine, vinorelbine,** etc.
- **Taxanes**: Originally derived from the *Taxus* pacific yew (now mostly synthetic). Kill cells by blocking microtubule disassembly.
  - M-phase specific (“spindle toxin”)
  - Radiosensitizing
  - Include **paclitaxel, docetaxel, cabazitaxel,** etc.

- **Topoisomerase Poisons**: Topoisomerases normally cut, twist, and re-ligate DNA. Topoisomerase poisons prevent re-ligation, leading to double-strand breaks.
  - Partially S-phase specific (can also kill cells during RNA synthesis)
  - Not so radiosensitizing
  - Include **etoposide, topotecan, irinotecan,** etc.
- **Hormonal Therapies**: Direct or indirect inhibition of hormones or hormone receptors.
  - Can only kill hormone-dependent cells (e.g., prostate and breast)
  - Include **tamoxifen, raloxifene, anastrozole, letrozole, exemestane, finasteride, dutasteride, bicalutamide, flutamide, leuprolide, goserelin, ketoconazole, abiraterone,** etc.

Targeted Therapies

- Each of these drugs is designed to inhibit a specific molecular pathway or family of pathways.
- **Monoclonal Antibodies** (-mabs): These bind a specific protein. They are very bulky and cannot cross the blood–brain barrier or the cell membrane.
  - Include cetuximab, trastuzumab, pertuzumab, bevacizumab, rituximab, tositumomab, ibritumomab, brentuximab, alemtuzumab, etc.
- **Tyrosine Kinase Inhibitors** (**TKI**s, -ibs): Small molecules that inhibit multiple tyrosine kinases involved in cell survival and growth signaling.
  - Include lapatinib, erlotinib, gefitinib, sunitinib, sorafenib, imatinib, dasatinib, ruxolitinib, crizotinib, vemurafenib, etc.
- **Other Inhibitors**: Inhibition of enzymes that are not tyrosine kinases.
  - Include sirolimus, everolimus, bortezomib, olaparib, vorinostat, thalidomide, lenalidomide, etc.
- **Receptor Agonists**: Activates rather than inhibits receptors.
  - Include bexarotene
- **Immunotherapies**: Activates immune system to fight cancer cells.
  - **CTLA-4** and **PD-1** are T-cell surface receptor proteins that act as immune checkpoints and prevent the indiscriminate attacking of cells by the immune system. T cells respond to the CTLA-4 and PD-1 ligands by decreasing production of inflammatory cytokines (interferon, interleukins), inhibiting T-cell growth, and reducing cytotoxic function.
  - Tumors can evade the immune system by expressing PD-1 ligand molecules such as PD-L1 and PD-L2 on the tumor cells, which downregulate/suppress the immune response.
  - **Anti-CTLA-4 antibodies** block the negative immune signaling from the dendritic cells to the T cell in the lymph node which results in immune activation.
  - **Anti-PD-L1 antibodies** block the negative signaling between PD-L1 ligands on the tumor cells and the PD-1 receptor molecules on the T cells in the tumor microenvironment which results in antitumor immune system activation.

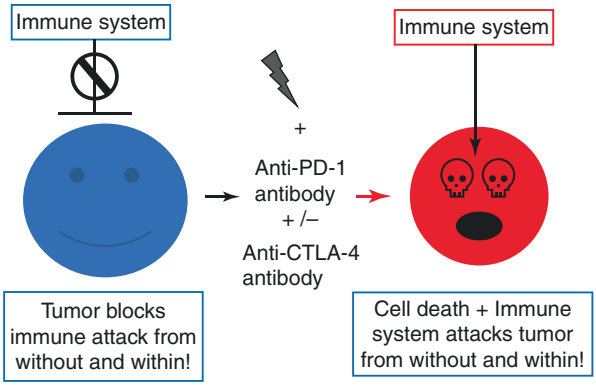

Fig. 31.1 Radiation combined with immune checkpoint inhibitors improves therapeutic response

  - Simultaneous treatment with anti-CTLA-4 and anti-PD-1 antibodies has been shown to improve immune antitumor response but also can increase toxicity.
  - Irradiation of tumors is now believed to not only induce tumor cell death but also activate immune stimulatory signals by releasing DNA fragments, neoantigens, ATP, HMGB-1, interferon, and pro-death signaling in tumor cells.
  - Radiation plus anti-CTLA-4 and/or anti-PD-1/PD-L1 antibody treatment has shown improved response in some solid tumors (see Fig. 31.1)
- **Cancer vaccines** include **sipuleucel-T** and **algenpantucel-T**. There are also promising developments against melanoma where the vaccines target genetically altered molecules on the tumor cell surface to trigger an immune response.

The Oxygen Effect for Chemotherapy

- Some drugs act through free radicals, and therefore require oxygen to work, just like radiation.
  - Include **bleomycin, procarbazine, and dactinomycin**
- Other drugs are more active under hypoxic conditions.
  - Include **mitomycin C, doxorubicin,** and **tirapazamine**
- Many chemotherapy drugs do not have any oxygen interaction.
- However, just like oxygen, many drugs are limited by diffusion distance and cannot penetrate a poorly vascularized tumor.

Multiple-Drug Resistance

- The theory of multiagent chemotherapy states that combining drugs with different modes of action makes it less likely for cancer cells to develop resistance.
- However, cancer cells often develop resistance to many drugs at the same time.

- Known mechanisms include the following:
  - **Membrane Channel Pumps**: The multiple-drug resistance (MDR) gene encodes a protein that ejects toxins from the cell, capable of binding multiple classes of drugs.
  - **Free Radical Scavengers**: Overexpression of glutathione-producing or -restoring genes can increase the cell's capability to repair free radical damage.
  - **DNA Repair**: Overexpression of DNA repair pathway proteins can overcome DNA-damaging agents such as alkylators and platinum.

Concurrent Chemotherapy and Radiotherapy

- Agents with **additive** cell kill: Killing is roughly equal to simple logarithmic addition.
  - **Example**: Radiation alone gives a one-log kill (SF = 10%), 5-FU alone gives a one-log kill (SF = 10%), concurrent 5FU-RT gives a two-log kill (SF = 1%).
- Agents with **synergistic** cell kill: Killing is significantly greater than simple logarithmic addition.
  - **Example**: Radiation alone gives a one-log kill (SF = 10%), gemcitabine alone gives a one-log kill (SF = 10%), concurrent gem-RT gives a four-log kill (SF = 0.01%).
- No **cross-resistance**:
  - Chemotherapy-resistant cells may not be resistant to radiation.
  - Radiation-resistant cells (hypoxic, S-phase, mutant p53) may be more sensitive to chemotherapy.
- **Reoxygenation**:
  - Chemotherapy may indirectly (through tumor shrinkage) or directly (bevacizumab) promote oxygenation of tumor.
- **Selectivity**:
  - In order to be clinically useful, a systemic agent must have greater cytotoxicity for tumor than for normal tissue.
  - Similarly, a useful radiosensitizer should have greater sensitization of tumor than normal tissue.

Photodynamic Therapy

- **Psoralens**, **porphyrins,** and **aminolevulinic acid (ALA)** are activated by specific wavelengths of visible or UV light, generating toxic-free radicals.
  - Visible and UV light can only reach very superficial lesions.
  - Commonly used for cutaneous malignancies (basal, squamous, and lymphoma) and endoscopic ablation of esophageal lesions.

Gene Therapy

- Types of anticancer gene therapy:
  - Introduce genes into healthy T cells or dendritic cells to boost antitumor immunity.
  - Introduce tumor suppressor genes into cancer cells to discourage growth.
  - Introduce "suicide" genes that selectively kill cancer cells.
  - Introduce "suicide" genes that are selectively activated by irradiation.
  - Introduce immunogenic genes into cancer cells to provoke antitumor immunity.
- Methods to introduce genes into human cells:
  - **Physical**: Electroporation and ballistic (can only be done ex vivo, such as in apheresis WBCs).
  - **Plasmid**: DNA sequences coated with lipid or polymer envelope that promotes uptake by cells.
  - **Viral**: Modified retrovirus, adenovirus, lentivirus, or herpes virus. Virus has to be resilient enough to evade immune system but not so resilient that it reactivates and kills the patient.
- As of 2014, gene therapy is not yet standard of care for any human tumors.
- **Synthetic Lethality** (see Chap. 21)
- **Synthetic lethality** is the term used to describe the scenario when the combination of perturbation of two genes or pathways by mutation, epigenetic change, or drug treatment results in cell death.
  - Inactivation of the DNA double-strand break (DSB) repair gene BRCA1 (Chap. 21) and BRCA2 tumor suppressor genes in human tumors can result in sensitivity to chemical inhibition of the poly(ADP-ribose) polymerase PARP involved in the repair of radiation-induced DNA single-strand breaks (SSB).
  - Inhibition of PARP results in PARP being trapped at the DNA single-strand break sites, which inhibits SSB repair and blocks DNA synthesis/replication.
  - Tumor cells can resolve the block by inducing a DNA DSB at that site. However, BRCA-deficient cells are unable to efficiently repair these lethal DNA DSBs resulting in dramatically increased cell death (see Fig. 31.2).
  - Radiation induces large numbers (thousands per Gy) of DNA SSBs which are normally easily repaired and smaller numbers of DSBs (~40 per Gy) which are lethal if not repaired. Chemotherapy can induce DNA strand breaks, adducts, and crosslinks.
  - Investigations into combining PARP inhibitors with radiation and chemotherapy are underway.

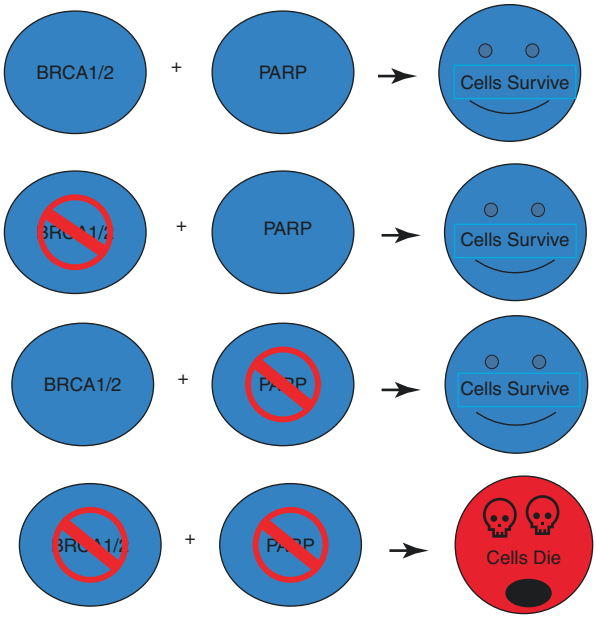

Fig. 31.2 Synthetic lethality between a mutated BRCA1/2 DNA DSB repair protein and inhibition of PARP, a protein involved in DNA SSB repair

Biology of Brachytherapy, Particle Therapy, and Alternative Radiation Modalities

32

Introduction

Most radiation therapy is delivered by linear accelerators capable of photon and electron irradiation. However, alternative modalities may have advantages in some clinical situations. Brachytherapy is radiation delivered by a radioactive source placed within or in close contact to the target, causing a rapid dose falloff with distance. Brachytherapy is classified as low dose rate (LDR) or high dose rate (HDR) and sealed or unsealed sources. Unsealed sources are free-floating radionuclides that can be injected into an anatomical space or administered systemically. Heavy charged particles include protons and heavy ions. These charged particles exhibit a high-dose Bragg peak, with little to no exit dose beyond the intended depth of treatment. Protons have an RBE approximating photons; however, heavy ions have a much higher RBE. Neutron beam therapy has a very high RBE, allowing for a greater effect on radioresistant tumors but also greater normal tissue toxicity. Boron-containing drugs may react with neutrons to further increase radiation dose to tumor.

Brachytherapy Definitions

- **Brachytherapy**: Radiotherapy delivered using nuclides placed within or in contact with the target volume
- **Sealed Source**: Fully encapsulated
  - **Low Dose Rate (LDR): ≤2 Gy/h**
    Temporary
    Permanent
  - **Medium Dose Rate (MDR): 2–12 Gy/h**
    Almost never used for clinical treatment
  - **High Dose Rate (HDR): >12 Gy/h**

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  - **Pulse Dose Rate (PDR): HDR** treatment for a few minutes every hour, such that the dose rate averaged over days is in the **LDR** range
- **Unsealed Source**: Brachytherapy using freely floating radionuclides (injected into a specific location, or administered systemically)

A Note on Brachytherapy

- Biologically speaking, there are several major differences between brachytherapy and EBRT:
  - **Dose Rate**: **EBRT** (excluding TBI) is usually performed at high dose rate. **Brachy** may be **HDR**, **LDR,** or **PDR**.
  - **Dose Gradient**: Most **EBRT** plans attempt to achieve a uniform dose within the target volume. **Brachy** always produces steep dose gradients.
  - **Fractionation**: **Brachy** is performed in far fewer fractions compared to **EBRT**.
    LDR implants may be performed in a single procedure (especially permanent implants).

Brachytherapy: Dose Rate Effects

- To a first approximation, the **LDR** survival curve is equal to the survival curve of **many small fractions** of EBRT/HDR.
  - This is the biological rationale for the use of **PDR** therapy.
- **Classic Dose Rate Effect: LDR** treatment results in decreased cell killing and no shoulder on the survival curve, compared to **HDR/EBRT**.
  - The magnitude of this effect directly correlates with the amount of **sublethal damage repair** (**SLDR**) in that cell type.
    This is responsible for differential sparing of normal tissue with **LDR** and is the biological rationale for the superiority of **LDR**.
  - Intrafraction repair goes from 0% to 100% between dose rates of **1 Gy/min** and **0.01 Gy/min** (**60 cGy/h**) (Fig. 32.1).
- **Inverse Dose Rate Effect:** In some rapidly cycling cells, cell killing actually increases between ~154 and ~ 37 cGy/h. This is a cell cycle effect.
  - At 154 cGy/h, the cell cycle is completely arrested, so radioresistant **S**-phase cells are radioresistant.
  - At 37 cGy/h, the cell cycle is allowed to progress into the radiosensitive **G_2/M**, causing cell killing.
  - This is another rationale for the superiority of **LDR**; proliferating cancer cells sensitize themselves, but non-proliferating cells do not.
- **Very Low Dose Rate**: Below the "critical dose rate," fast-growing cells are able to repopulate faster than they are killed.
  - For example, mouse jejunum treated at <0.54 cGy/min (**32 cGy/h**) shows very little killing.

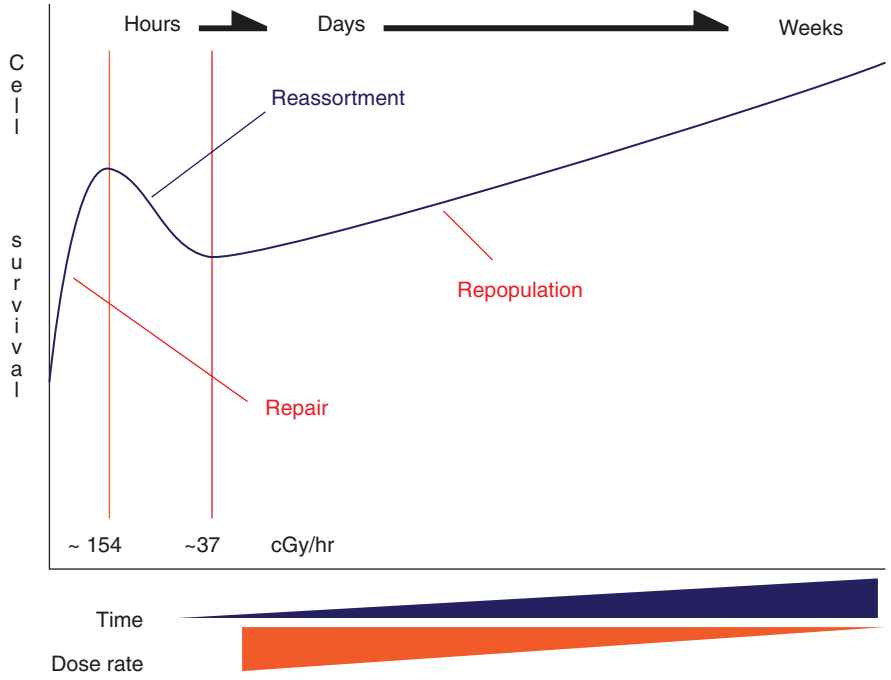

Fig. 32.1 Dose rate to cell survival curve that illustrates the general improvement in cell kill with increasing dose rate with the exception of the region containing the inverse dose rate effect

- **Permanent implants** have an extremely low dose rate. Therefore, they are ineffective on rapidly proliferating tumors.
  A typical **I-125** prostate seed implant has a dose rate of **~7 cGy/h**. Fortunately, prostate CA is a very slowly proliferating tumor.

Dose Rate and Clinical Endpoints

- **Mazeron** did two studies on interstitial **LDR** implants: one on the oral cavity and one on the breast.
  - **Oral Cavity**: Dose rates <50 cGy/h were associated with less necrosis, with similar local control as long as total dose was adequate.
  - **Breast**: Between 30 and 90 cGy/h, higher dose rates were associated with improved local control.
- Typical temporary implant **LDR** dose rates are 50–60 cGy/h to the prescription point. However, higher or lower dose rates may be used depending on clinical judgment and implant geometry.
  - Higher dose rate = more efficacy, more toxicity.
- Permanent implant **LDR** dose rates are variable, and mostly depend upon which isotope is being used.

  - Shorter half-life = higher dose rate.
- Dose rate effects are **largely irrelevant** for **HDR**, as the dose rate is too high to allow intrafraction repair or reassortment.

Brachytherapy: Choice of Nuclide and Implant

- **Ra-226** was used for many decades but is almost never used anymore due to risk of radon leakage.
- **Permanent LDR** implants generally use **I-125**, **Pd-103**, or less commonly **Au-198**.
- **Temporary LDR** implants may use **Au-198, Ir-192**, **Cs-137**, **Co-60**, or others.
- **HDR** implants almost always use **Ir-192**.
- Implants are classified as **interstitial** (such as prostate or breast brachy) or **intracavitary** (such as GYN brachy).
- See Chap. 11 for a more detailed discussion of brachytherapy techniques.
- See Appendix B for information on nuclide origins, energies, and half-lives.

Unsealed Sources

- **I-131** is a beta emitter that is taken up by thyroid tissue as well as differentiated thyroid cancers.
- Bone-seeking nuclides include **Sr-89**, **Sm-153**, and **Ra-223** and are used to treat widespread bony metastases.
- **P-32** is a beta emitter that can be used to treat the lining of a cyst, joint space, or body cavity.

Radioimmunotherapy (RIT)

- Radionuclide-antibody conjugates are used to target high doses of radiation specifically to tumor.
  - **I-131** is a mixed beta/gamma emitter.
  - **Y-90** is a pure beta emitter.
- **I-131 Antiferritin** and **Y-90 Antiferritin**: Targets ferritin-rich tumors such as Hodgkin lymphoma and hepatocellular carcinoma.
- **Y-90 Ibritumomab Tiuxetan (Zevalin)**: Targets CD20 (like rituximab), used to treat rituximab-refractory non-Hodgkin lymphoma.
- **I-131 Tositumomab (Bexxar)**: Also targets CD20 and has been used for recurrent and refractory non-Hodgkin lymphoma.

Proton Beam Therapy (Also See Chap. 18)

- Protons are used for their **Bragg Peak** - > no exit dose and greatly decreased integral dose.
  - Advantages are mostly physical not biological; however, new data suggest different genes may be induced after proton versus X-ray treatment (Fig. 32.2).
- Biological effectiveness is very close to photons, with a standard **RBE = 1.1** (in Co-60 Gy equivalents).
  - **OER** = same as Co-60 photons.
- The RBE of the back edge of the proton Bragg peak is not well defined, but data suggest it could be much higher than RBE = 1.1 (in the range of RBE = ~1.6).
  - Therefore, the distal edge of a proton beam should not be placed inside a critical normal structure.
- A single ("pristine") Bragg peak is too narrow to treat anything, so therapeutic proton beams use a spread-out Bragg peak (**SOBP**) with multiple Bragg peaks at different ranges.
  - The entry dose of the **SOBP** is much higher than that of a pristine Bragg peak.
- Proton beams are produced by cyclotrons, which are much larger and more expensive than linacs.

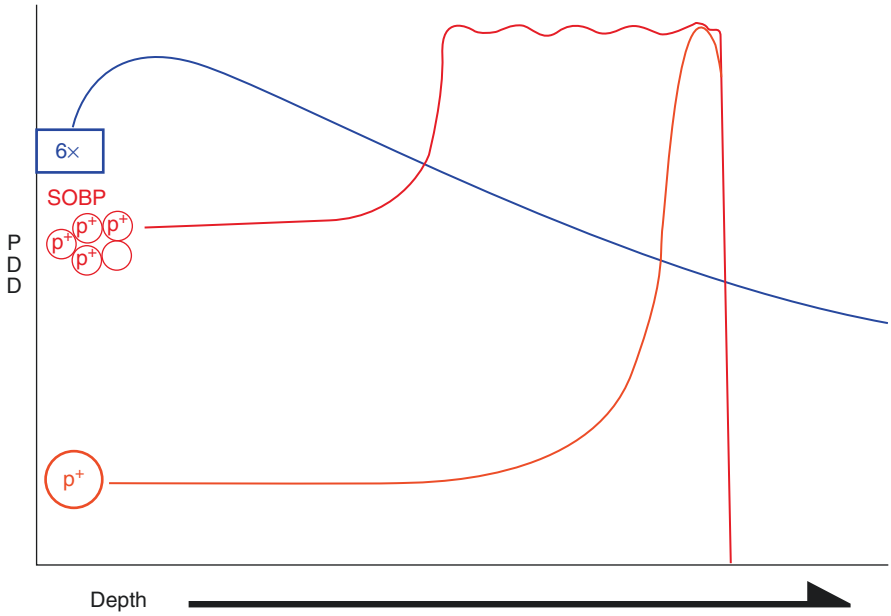

Fig. 32.2 Comparison of dose profiles between 6 MV photons (*blue*), a pristine Bragg peak from a monoenergetic proton beam (tan), and a poly-energetic proton beam illustrating a spread out Bragg peak (*red*)

- As of 2020, there are more than 35 proton facilities in the USA with most being in the 230–250 MeV/n energy range with spread beam and pencil beam scanning capability.

Fast Neutron Therapy

- A **fast neutron** is approximately ≥6 MeV.
- **Neutrons** were used for their low OER (ability to kill hypoxic cells) and high RBE in specific tumor types (such as salivary gland tumors).
  - Neutrons can achieve higher local control of salivary gland tumors when compared to photons.
  - Unfortunately, they also have dramatically worse late toxicities, limiting their clinical use.
- Neutrons are an uncharged particle, so they do not have a Bragg peak.

Boron Neutron Capture Therapy (BNCT)

- **Boron** absorbs **slow neutrons** (0.025–10 keV) and fragments into alpha particles, delivering a very high dose locally.
- Must pretreat with a boron-containing drug that selectively localizes to tumor.
- Slow neutrons have very poor penetration of tissue and can only treat superficial tumors (approx. 2–3 cm).

Heavy Ion Therapy

- **Heavy ions** are defined as charged particles heavier than a proton. **Carbon-12** is the most popular heavy ion.
- **Carbon-12** and other **heavy ions** have **high-LET** biological effect, as well as a **Bragg peak**.
  - Both physical and biological advantages.
  - The RBE of carbon ion RT therapy versus photons has been estimated to be 1.6–3.0 depending on treatment volume and tumor type.
  - The OER of carbon ion RT therapy versus photons also appears to be lower.
  - **High RBE** and **low OER** may help overcome tumor hypoxia and radiation resistance such as in pancreatic cancer.
- Effective dose in **Bragg peak** is not well defined. Both physical dose and RBE are greatly increased.
  - There is great uncertainty about the efficacy and long-term toxicity of heavy ion therapy.

- Heavy Ions are accelerated by synchrotrons, which are even larger and more expensive than proton beam cyclotrons.
  - As of 2020, carbon heavy ion therapy is not available in the USA even though heavy ion therapy was pioneered at the Lawrence Berkeley laboratory in California in the 1980s.
  - Japan, China, Germany, and Austria have carbon-based heavy ion facilities.

Hyperthermia

33

Introduction

Though its use has waned and conventional heat treatments alone are only used to treat some types of cancer at a few clinics in the United States, there is still some interest in the use of hyperthermia as an adjuvant to radiotherapy, since it can often work synergistically with ionizing radiation to enhance tumor control. There are several methods by which heat may be delivered to a tumor, but with the general exception of some superficial tumors, hyperthermia remains technically difficult to accurately and uniformly administer, and monitoring of the heat doses remains problematic. Also, the development of thermotolerance is a barrier to its use as a stand-alone therapy, and also precludes the use of multiple heat treatments when used as an adjuvant to fractionated radiotherapy. While radiation typically induces death via damage to DNA, heat is believed to induce cell death through denaturation and aggregation of proteins. Hyperthermia may be effective at killing radio-resistant tumor cells, including S-phase, nondividing, hypoxic, or poorly vascularized cells. When combined with radiation, there may be a synergistic effect through vasodilation (reducing hypoxia) and inhibition of DNA repair (double-strand breaks). After a heat dose, thermotolerance may develop due to expression of heat-shock proteins. While interest in conventional hyperthermia has waned, thermal ablation (using temperatures >50 C) may produce good long-term results.

Definition of Hyperthermia and Thermal Ablation

- **Hyperthermia** is generally regarded as the use of temperatures between 39 °C (102 °F) and ~ 45 °C (113 °F) to achieve selective cell killing. It may be used alone or in combination with radiotherapy, chemotherapy, or both.
- In the context of radiation biology, conventional **hyperthermia** is not used with the intent to "cook" the tumor. However, **thermal ablation**, which involves the

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use of very high temperatures in the range of ~50 °C (122 °F) to 100 °C (212 °F) may essentially result in coagulation of tumor tissue.

Rationale for Hyperthermia

- Hyperthermia has been used to treat superficial tumors, more commonly in Asia and Europe, and has also been used for palliative purposes. However, use of hyperthermia has mostly been explored as a potential adjunct to radiation therapy, because hyperthermia and radiation may produce additive or synergistic effects depending upon the sequencing of the two treatments, leading to more complete and partial responses:
  - There are no intrinsic differences between tumor and normal cells with respect to hyperthermic sensitivity. However, extrinsic differences are exploitable.
  - Poorly vascularized tumors may be easier to heat than well-vascularized normal tissue.
  - Hypoxia and low pH may increase sensitivity to hyperthermic killing (Fig. 33.1).
  - Late S-phase cells (which are most resistant to radiation) are most sensitive to hyperthermia.

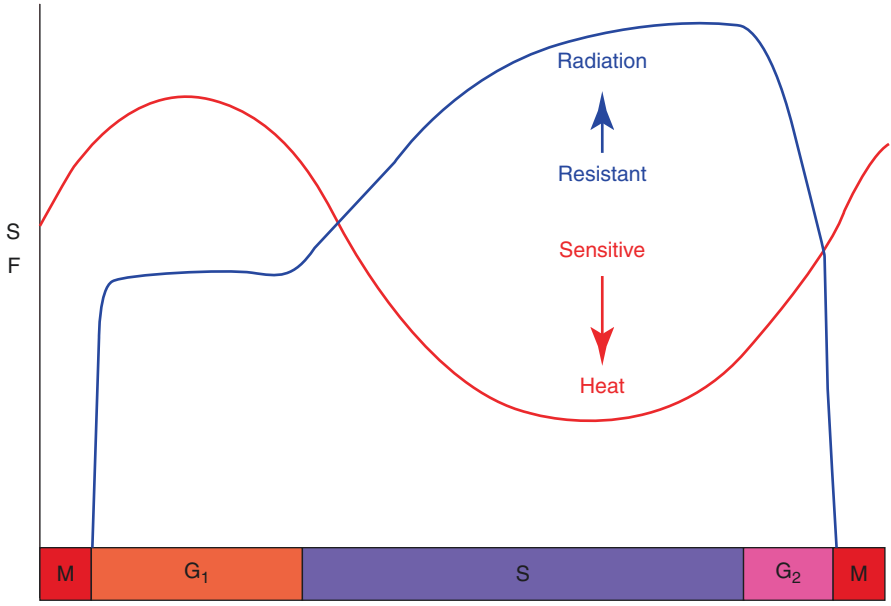

Fig. 33.1 Sensitivity (as indicated by relative surviving fraction) of cells throughout the cell cycle to radiation (*blue*) or hyperthermia (*red*)

Cytotoxicity of Heat

- Heat damages cells by denaturing and inducing aggregation of proteins. Denaturation and aggregation of nuclear proteins may inhibit repair of radiation-induced DNA damage (inhibition of double strand break (DSB) repair has been advanced as the mechanism by which heat sensitizes cells to radiation, see below).
  - This mechanism of cell killing is unlike that observed after irradiation, where death may result from DSBs, and subsequently, exchange-type chromosome aberrations.
  - An Arrhenius plot is constructed when $1/D_0$ is plotted as a function of 1/T (with T in degrees kelvin). The slope provides the activation energy involved in cell killing. Since the activation energies for cell killing and protein activation are similar, the target for heat-induced cell killing may be a protein or a subset of proteins.
- Late S-phase cells are most sensitive to hyperthermia (S-phase is also the most radio-resistant phase).
- Heat damages cells to a greater extent when there is less blood vasculature to act as a heat sink to cool the tumor (hypoxic or poorly vascularized cells are more radio-resistant).
- Hyperthermia kills nondividing cells as well as dividing cells (unlike radiation which generally only kills dividing cells).
- Cell killing is **much** higher with concurrent heating and irradiation, compared to sequential heat and RT. However, this is often impractical clinically.
  - Two mechanisms of heat radiosensitization:
    Vasodilation (decreased hypoxia)
    Inhibition of repair of radiation-induced DNA damage, mostly, importantly, DNA double-strand break repair

Heating and Temperature Monitoring

- Heat treatments may be administered externally or using an implantable device inside the tumor using the following techniques:
  - Hot water bath
  - Insulated suit or chamber + infrared radiation
  - Microwaves
  - Short-wave diathermy
  - Radiofrequency-induced currents
  - Ultrasound
- The heat source may be applied systemically or in a localized fashion:
  - Systemic: Total-body hyperthermia
  - Localized External: Heat source directed toward the tumor
  - Localized Internal: Heat source implanted within the tumor

- Temperature should be monitored at multiple points, as heating is often nonuniform.
- Primary limitation of heat therapy is the technical limitation:
  - Applying heat selectively to and uniformly throughout the tumor while sparing normal tissues
  - Applying heat within the proper time frame of radiation therapy
  - Reducing invasive techniques, especially if they would be required on a daily basis
  - Expensive devices or power requirements
- Another limitation is the inability to achieve uniformity (some areas will be heated more than others) due to thermal diffusion of tissue.
  - Heat can be carried away by the heat-sink effect of venous blood flow (think of water-cooled machinery).
  - Heat-sink effect has a slight benefit to normal tissues, so they will not receive as much heat as tumor cells, and tumors that do experience vasodilatation can become better oxygenated, but this makes heat dosing logistically difficult.
- Overall, hyperthermia has many benefits but is so technically difficult that it is usually reserved for academic studies or for superficial tumors (melanoma, neck nodes, or superficial breast cancers) or recurrent tumors. Even in these cases, it is not standard of care.
- The main barrier to uniform heating is the **heat-sink** effect; venous blood effectively carries away the heat.

Heat in Tumors Versus Normal Tissues

- Tumors may receive a higher dose of heat because they are poorly vascularized and do not enjoy the **heat-sink** effect of normal blood flow.
- Normal tissues are able to vasodilate and increase blood flow to get rid of heat; many tumors cannot, or may even suffer decreased blood flow.
- Tumors have a high prevalence of hypoxia and cells in the tumor are growing at an acidic pH; both of these factors can increase heat-related cytotoxicity.

Thermal Dose

- **Thermal dose** is expressed as **cumulative equivalent minutes at 43 °C to 90% of monitored points (CEM 43 °C T_{90})**.
- Above 43 °C, treatment time needs to decrease by a factor of 2 for each 1 °C temperature increase to achieve a similar biological effect (such as a specific surviving fraction).
- Below 43 °C, treatment time needs to increase by a factor of 4–6 for each 1 °C temperature increase.

Thermal Enhancement Ratio (TER)

- **TER** is a **ratio of radiation doses** that achieve the same endpoint in the absence and presence of heat:

$$\text{TER} = \frac{\text{Dose}\ \left(\text{No heat}\right)\ \text{to cause an effect}}{\text{Dose}\ \left(\text{With heat}\right)\ \text{for same effect}} \tag{33.1}$$

- For a **1 h CEM 43 °C T_{90}** hyperthermia treatment:
  - **TER ≈ 2.0** (normal tissue).
  - **TER ≈ 4.3** (tumor)
- Theoretically, this means that a **2 Gy fraction** with heat (**1 hour CEM**) is equivalent to **4 Gy** to normal tissue, and **8.6 Gy** to tumor.

Heat-Shock Proteins and Thermotolerance

- Exposure of cells to heat induces the expression of **heat-shock proteins (HSPs)**, an adaptive (protective) response to heat.
- Onset and decay of **thermotolerance** (transient resistance to heat killing) correlates with appearance and disappearance of HSPs. Thermotolerance is a transient but not heritable resistance to subsequent heat treatment.
  - For exposure to low-temperature hyperthermia (**39–42.5 °C**) cells can become thermotolerant during a prolonged heating period, thus resulting in a plateau of the survival curve.
  - For high-temperature hyperthermia (**43–47 °C**) cells exposed to brief heat treatments may become thermotolerant and more resistant to a second exposure during post-heat incubation at 37 °C for several hours to days between exposures.
- **Thermotolerance** may last for up to 1–2 weeks in vivo, and is believed to greatly decrease the effectiveness of fractionated thermal killing in the clinic.
  - For this reason, hyperthermia protocols usually only include one to two heat treatments per week.

Hyperthermia and Radiotherapy

- Heat alone is rarely capable of producing consistent responses in most human tumors, for several reasons:
  - Difficulty of uniformly heating a macroscopic deep-seated tumor volume.
  - Difficulty of accurately measuring the temperature within the tumor.
  - Thermotolerance after the first heat fraction.

- Therefore, since it has been demonstrated in vitro and in vivo that heat sensitizes mammalian cells to ionizing radiation, hyperthermia is sometimes combined with radiotherapy to increase the therapeutic ratio.
- Clinical hyperthermia protocols have used temperatures of **41–43 °C**, with a goal of **1 h CEM 43 °C T_{90}** delivered once or twice a week.
- Theoretically, hyperthermia should work best if given simultaneously with RT. For practical reasons (interference of RT machines with hyperthermia machines), it is usually given immediately before or after.
- Low temperature **(41 °C)** hyperthermia has been shown to improve the oxygenation of hypoxic tumors.

Hyperthermia: Difficulties

- **Uniform Heating:**
  - Very easy to get cold spots where blood flow carries away heat. May also get hot spots in poorly vascularized areas.
  - A small difference in temperature (**1 °C**) causes a two- to sixfold change in equivalent thermal dose (**CEM**).
  - Most heating devices must be in contact or close proximity to the tissue being heated.
    Difficult to heat deep-seated tumors.
  - Temperature monitoring is often difficult and requires multiple invasive probes.
- **Timing:** For best results, tumor must be heated during, or immediately before or after RT, but substantial heat-radiosensitization may occur when heat is administered even several minutes after irradiation, due to inhibition of sublethal damage repair (inhibition of DSB repair).
- **Interference** between heating and radiotherapy equipment:
  - Microwave and radiofrequency heating devices give off electromagnetic interference that can harm other equipment, such as radiotherapy linear accelerators; therefore, they cannot be used in the same room.
  - Moving the patient from the hyperthermia suite to the radiotherapy vault or vice versa presents a logistical challenge.
- Heat works best if given in 1–2 fractions per week, while radiation works best when given in many small daily fractions.

Stochastic, Deterministic, and Heritable Effects (and Some Radiation Protection Basics)

34

Introduction

Radiation carcinogenesis is considered a stochastic effect, and is modeled by the linear no-threshold (LNT) model. The excess risk of dying from a radiation-related cancer (above the natural baseline) is based on age at exposure, gender, total dose, and dose rate. Secondary leukemias may show up after just a few years with a decrease in incidence after about a decade, while secondary solid tumors typically occur after a decade or more. Cataractogenesis was long-regarded as a deterministic late effect (since deterministic effects are usually associated with a dose threshold), but there has been much debate about this in recent years. Genetic risk is associated with increased rate of mutations in the offspring of irradiated animals. It is generally recommended that humans avoid planned conception for at least 6 months after receiving radiation to the gonads. For radiation protection purposes, recommended dose limits for stochastic, deterministic, and heritable effects are often expressed in Sv, taking into account dose, type of radiation, and the specific tissue. Equivalent dose is defined as physical dose multiplied by a weighting factor, correcting for the type of radiation. Effective dose is defined as equivalent dose multiplied by tissue weighting factor, correcting for the volume of tissue irradiated.

Deterministic and Stochastic Effects

- A **deterministic** (non-random) **effect** occurs after exceeding a threshold dose, and the severity of the effect correlates with the dose. In radiation protection circles (e.g., NCRP and ICRP), these effects are more recently being referred to as "tissue reactions." The term is associated with effects that result from damage to many cells.
  - Example: radiation-induced skin erythema.

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- A **stochastic** (random) **effect** occurs randomly with a probability that is proportional to dose, and the severity of the effect is not dose-dependent (either happens or it does not, although incidence in a population is dose-dependent). No threshold dose!
  - Examples: Both primary and secondary radiation-induced malignancies and heritable mutations are stochastic effects.

Equivalent Dose and Effective Dose

- Absorbed dose is measured in **Gy**, but this does not take into account the type of radiation or the type of tissue irradiated.
- For radiation safety purposes, dose is multiplied by a **weighting factor (WF)** that corrects for the type of radiation.
  - This number is known as **equivalent dose** and is measured in **Sieverts (Sv)**.
  - **WF** varies with type of radiation:
    Photons and electrons, **WF = 1**.
    Protons, **WF = 2**.
    Neutrons, **WF varies, up to 20**.
    Heavy ions, **WF = 20**.
- In addition, partial-body exposures can be multiplied by a **tissue weighting factor (W_T)** to obtain an **effective dose**.
  - **Effective dose** is also measured in **Sv** but depends upon the volume of tissue irradiated.
- So let us say a chest X-ray gives **0.5 mGy** to the chest:
  - The **equivalent dose** is **0.5 mSv** to the chest.
  - The **effective dose** is closer to **0.1 mSv** (approximately—the real number actually depends on male vs. female, due to breasts).

Dose Response for Radiation-Induced Cancers

- The **linear no-threshold (LNT)** model assumes a direct linear relationship between dose and carcinogenesis.
- This is in contrast to dose–response models that have a threshold beneath which radiation carcinogenesis does not occur.
- Radiation hormesis models hypothesize that extremely low doses of radiation may actually be beneficial (Fig. 34.1).
- The current human evidence is insufficient to either prove or disprove the existence of a threshold.
  - The **LNT** model is the most conservative approach, so it is used for radiation protection purposes.

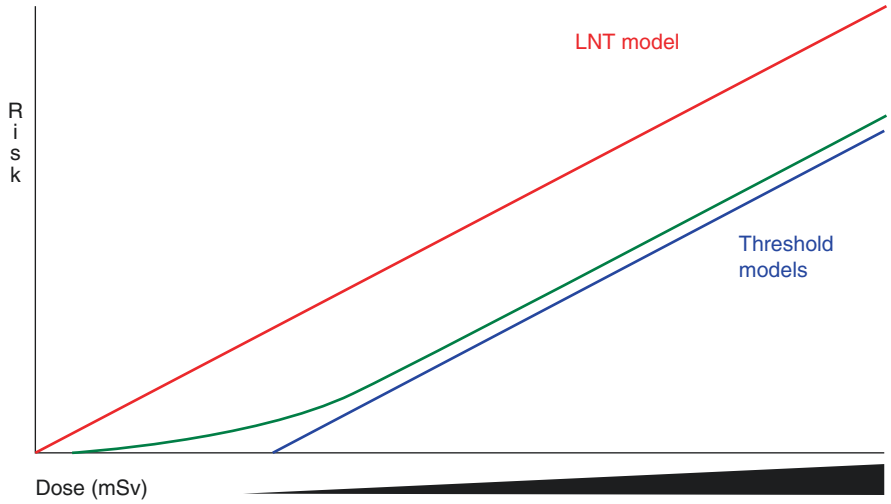

Fig. 34.1 Cancer risk to dose models including linear no-threshold model (*red*) and linear threshold models (*blue*). The true cancer risk from low doses of radiation may more closely resemble the shape of the *green curve*

Mechanism of Carcinogenesis

- Ionizing radiation causes double-strand breaks, leading to chromosomal aberrations, mutations, and genomic instability.
  - Aberrations may be lethal or may be permanently passed on to cellular progeny.
  - Cells that survive radiation with aberrations and genomic instability are believed to be involved in radiation-induced carcinogenesis.
- Radiation-induced mutations are typically **large-scale** deletions, duplications, translocations, or other chromosomal aberrations, or aneuploidy.
- Radiation can also cause point mutations (single-nucleotide polymorphisms, transitions, transversions, frameshifts, micro-deletions, or insertions).
  - These are more characteristic of random (sporadic) and chemical-induced mutations.
  - All of the above changes are considered genetic alterations.
- Ionizing radiation can also induce changes in gene promoter methylation. These are considered epigenetic alterations.
  - In general, if methylation of gene promoters is significantly increased, gene expression is suppressed. Conversely, if methylation of gene promoters is significantly reduced or completely lost, gene expression is induced.

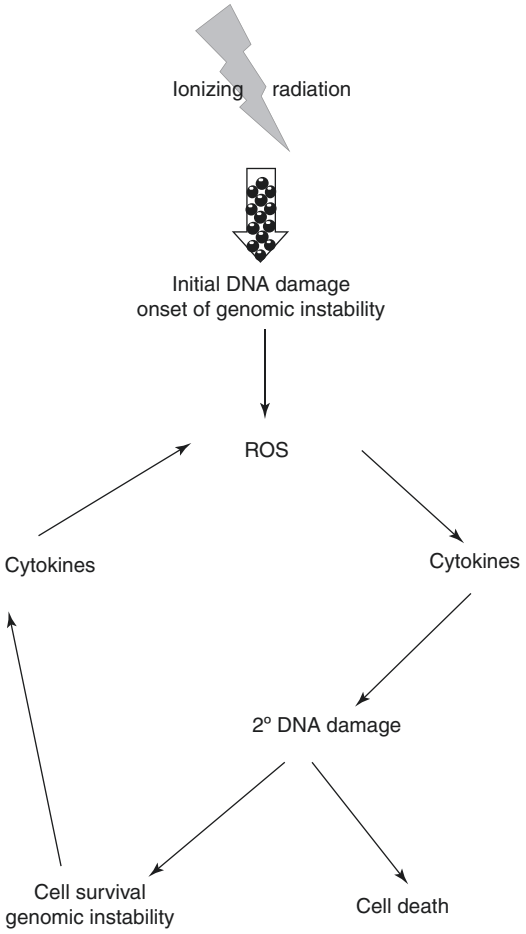

Fig. 34.2 The role of DNA damage, ROS, and cytokines in driving long-term radiation-induced genomic instability. (Based on concepts developed by W.F. Morgan, J.B. Little, C. Mothersill, and M. S. Mendonca)

- Sporadic and radiation-induced carcinogenesis involves activation of oncogenes and loss of tumor suppressor genes.
  - Oncogenes can be activated or overexpressed by both genetic and epigenetic mechanisms.
  - Tumor suppressor genes can be deleted or silenced by both genetic and epigenetic mechanisms.
  - These genetic and epigenetic changes can be delayed and caused by radiation-induced genomic instability driven by ROS and cytokine cycles (TNF-α and TGF-β, etc.) over many years (Fig. 34.2).

Radiation Protection Organizations

- The **Biological Effects of Ionizing Radiation (BEIR)** Committee is an academic committee devoted to the basic science behind radiation protection.

- The **United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)** is a reporting and regulatory agency.
- The **International Commission on Radiation Protection (ICRP)** is an advisory agency.
- The **National Council on Radiation Protection and Measurements (NCRP)** is a US council chartered by the US Congress that advises and publishes reports and recommendations.
- The only large consistent set of **epidemiological data** for long-term effects of radiation exposure had been the **Japanese atomic bomb survivors; however, a great deal of data are now being generated by individuals exposed as a result of the Chernobyl disaster (e.g., increased risk of thyroid cancer in children) and in occupational settings**.

Absolute and Relative Risk of Carcinogenesis

- Approximately, **40%** of all humans will suffer a malignancy at some point in their lifetime.
- For the vast majority of people exposed to radiation, the absolute risk of a **radiation-induced malignancy** is much smaller than the absolute risk of **sporadic malignancies**.
- The **BEIR** and **ICRP** models of radiation carcinogenesis assume that radiation is a **relative** modifier of malignancy.
  - That is, radiation multiplies the frequency of malignancy by a dose- and age-dependent factor.
  - This model implies that radiation-induced malignancies are likely to have an age and site distribution similar to sporadic malignancies, whether or not that is true.

Radiation and Chemotherapy Carcinogenesis

- Chemotherapy drugs are known to cause second malignancies, most prominently leukemia risk with alkylating agents.
- The **latency** of secondary leukemias is significantly **shorter** (few years) than solid tumors (decades).
- Combined chemotherapy and radiotherapy is likely to increase secondary malignancy risk.

Dose–Response Curves for Carcinogenesis

- Gray (1950s) studied leukemia induction after total-body irradiation in mice, and found a **bell-shaped curve** of carcinogenesis.
  - Increasing the radiation dose increases carcinogenesis risk only at low doses.

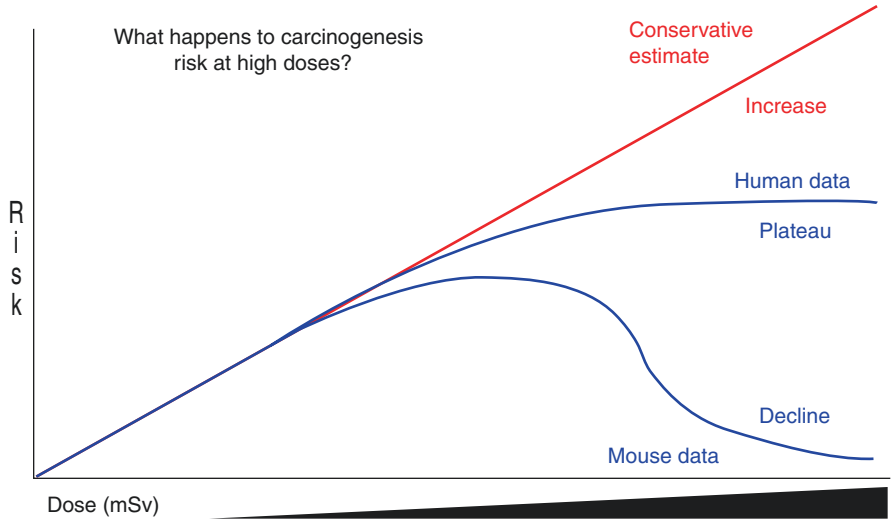

Fig. 34.3 At high doses, the LNT model predicts increasing incidence of cancer with increasing dose, but data suggest that this may not be the case

  - After 2 Gy or so, radiation is more likely to cause cell killing than mutation. Carcinogenesis risk plateaus and then declines (Fig. 34.3).
- Human data have suggested a plateau in dose–response after ~10 Gy, but there is no evidence of a decline at any dose.
  - Radiation protection estimates assume a **linear** relationship between dose and carcinogenesis, without any high dose plateau or decline.
  - Again, this is because a linear relationship is the most conservative estimate, not because it is the most biologically plausible.

ICRP Carcinogenesis Risk Estimates

- Carcinogenesis risk estimates were derived from Japanese nuclear bomb survivors who were irradiated with high-LET radiation at an extremely high dose rate.
- The dose and dose-rate effectiveness factor (**DDREF**) corrects for the decreased biological effectiveness of low-LET, low dose, and low dose rate irradiation.
  - **Low DDREF exposures** are defined as **low-LET** radiation with a dose rate less than **0.1 Gy/h**, or total dose less than **0.2 Gy** at any dose rate.
  - **High DDREF exposures** are **high-LET** radiation, or dose greater than **0.2 Gy** and dose rate over **0.1 Gy/h**.
- For the purposes of carcinogenesis, we should use **effective dose (Sv)**. This is an equivalent dose weighted for volume of tissue irradiated.
- According to **ICRP 60**, the total risk of radiation-induced malignancies is:
  - **10%/Sv** for entire population and **high DDREF**.
  - **8%/Sv** for working population and **high DDREF**.

  - **5%/Sv** for entire population and **low DDREF**.
  - **4%/Sv** for working population and **low DDREF**.
- The numbers are slightly lower for "working population" because children are excluded.
- The **ICRP** numbers are widely used to estimate the risk of secondary malignancies from diagnostic studies, airline screening X-rays, nuclear accidents, etc.
- **Example**: 80 million people are screened by airport X-rays, receiving **0.25 μSv** each. How many second malignancies do you expect?
  - $0.25 \times 10^{-6} \times 5\% =$ **1.25×10^{-8}**/person.
  - $1.25 \times 10^{-8} \times 8 \times 10^{7} =$ **1 secondary malignancy**.

Carcinogenesis Risk Estimates in Radiation Therapy

- The definition of a **Sv** uses linear weighting of dose by the volume and type of tissue irradiated:
  - **60 Gy** * tissue weighting factor **0.04 = 2.4 Sv**.
  - **20 Gy** * tissue weighting factor **0.12 = 2.4 Sv**.
- Whether this can be used to directly calculate second malignancy risk in radiotherapy patients is debatable:
  - **2.4 Sv * 8%/Sv = 19.2%** ICRP risk estimate (both cases).
  - However, you could argue that the true number is lower due to the "plateau effect" of high doses.
  - If so, 60 Gy to a small volume should be much less carcinogenic than 20 Gy to a large volume.

Carcinogenesis Risk and Age, Gender, and Time

- Compared to the whole population, an individual patient may have more or less risk of carcinogenesis based on several factors:
- **Age**: Children are much more susceptible to radiation-induced malignancy.
  - **Children < 5yo** are **~3×** more susceptible than the population average, or ~ **10×** more susceptible than older adults.
- **Gender**: Women are more susceptible to radiation-induced malignancy because of breast cancer.
- **Time**: Radiation-induced malignancies occur years to decades after irradiation. A patient with a short life expectancy is very unlikely to develop a radiation-induced malignancy.

Known Radiotherapy-Induced Malignancies

- **Prostate Cancer**: Compared to patients treated with surgery, patients treated with radiation had a 34% increased relative risk of second malignancy at 10 years.

  - The most common second malignancies were bladder and rectum.
  - The largest relative increase was in-field sarcoma.
- **Cervical Cancer**: Compared to patients treated with surgery, patients treated with radiation had increased risk of cancers of the bladder, rectum, vagina, uterus, cecum, bone, and non-Hodgkin lymphoma.
  - Younger age at time of irradiation correlates with second malignancy.
- **Hodgkin Disease**: Female HD survivors have a 3–17× increased risk of breast cancer compared to the general population.
  - Depending on age of irradiation, may have up to 50% lifetime risk of developing breast cancer.
  - **Second primary malignancies** are the most likely cause of death in long-term HD survivors.

Radiation-Induced Cataracts

- *Lens is essentially a self-renewing but closed tissue system* in which continuous division of **epithelial cells occurs**. These differentiate into lens fiber cells. However, differentiated *lens fiber cells must eliminate their organelles* and degrade DNA in order for the lens to remain *transparent*. Since damaged or irregular cells cannot leave the lens capsule, if **lens epithelial cells are** damaged after irradiation, any differentiated but *abnormal fibers that migrate to the posterior* subcapsule can contribute toward opacification of the lens.
- Radiation-induced cataracts often originate in the posterior subcapsular region of the lens, but not always, especially after high dose exposures. Cataracts that start in the posterior subcapsular region may remain as stationary cataracts or progress to the anterior subcapsular or other regions of the eye where it may become nonspecific and indistinguishable from cataracts induced by other means.
- The latent period for cataractogenesis is inversely related to dose (e.g., greater dose = shorter latent period).
- High LET radiations are more effective at inducing cataracts than low LET, so RBE would be higher.
- Prior to 2011, ICRP and NCRP categorized radiation cataractogenesis as a deterministic effect. Based on early datasets later deemed problematic for various reasons, ICRP originally had suggested 2 Gy as the threshold dose for radiation cataractogenesis. However, numerous new reports suggest that **there may be no dose threshold**, or at least that the threshold is much lower than the **2 Gy dose** originally estimated. NCRP recently reduced its recommendation for the new occupational annual lens dose limit to 50 mGy; the "Member of Public Annual lens of eye limit" was set at 15 mGy. Since some mechanistic studies support the notion that radiation cataractogenesis could be a stochastic process, but much of the epidemiological evidence currently available suggest a dose threshold, NCRP concluded that a threshold model be used for radiation protection purposes, but also concluded that it was not currently possible to estimate a threshold for lens effects.

Mental Retardation

- Doses of about *3.5–4 Gy to the embryo/fetus will usually cause a miscarriage* but when the fetus survives lower doses, then potential abnormalities may include *microcephaly that is* sometimes combined with mental retardation. Older data from A-bomb survivors suggest that maternal exposures as low as *6–19 cGy* may be sufficient to cause microcephaly. However, more recent data suggest that 0.01 Sv at 4 weeks postconception is enough to cause an excess incidence.
- T*he most sensitive period for mental retardation is 8–15 weeks after conception.*
- There appears to be a *linear relationship between incidence and dose* during this interval, but because of scant data, we cannot dismiss the possibility that a dose threshold may exist, which would mean the dose response could be nonlinear. The *shift in intelligence test scores has been estimated to be ~30 IQ points per Gray*.

Genetic Risks of Radiation: Animal Models

- Animal studies indicate a significant risk of inherited mutations in the progeny of irradiated animals:
  - **Fruit flies (*Drosophila*)** have a very high rate of inherited mutations.
  - **Mice** have a somewhat lower rate of inherited mutations.
- The **doubling dose** is defined as the dose of radiation required to double the spontaneous rate of mutations.
  - **0.05–1.5 Gy** in *Drosophila*.
  - **Approx. 1 Gy** in mice (due to the paucity of human data at low dose rate, this estimate for doubling dose is probably good for humans as well).
- The **megamouse study** irradiated millions of mice and observed their progeny for mutations at seven genetic loci. This led to the following conclusions:
  - Different genes showed great variability of radiosensitivity for heritable damage, with up to 35-fold variability.
  - There is a substantial dose-rate effect for mutation induction.
  - Most mutations are considered harmful, but radiation does not create new types of mutations that are not already seen in the general population.
  - The number of mutations that are produced is **proportional to dose**,
  - **Low dose rate** (0.8 cGy/min, 48 cGy/h) irradiation produced much less heritable damage than high dose rate irradiation (e.g., there is a dose-rate effect). The human mutation rate is likely to be lower than that in the mouse.
  - Mouse oocytes are much more radiosensitive than human oocytes, so data on females are difficult to extrapolate to humans. Mutability of male germ cells is several times greater than cells in the female.
  - Heritable damage is greatly decreased by allowing a time interval of several months to elapse between irradiation and conception (extrapolated to **6 months** for human males; unknown for females).

Genetic Risks of Radiation: Human Data

- According to **UNSCEAR** estimates, ~73% of humans have at least one harmful mutation (this includes "multifactorial disease" such as a family history of diabetes or hypertension).
  - It is difficult to observe radiation-induced heritable disease in humans because the baseline prevalence for anomalies is so high.
  - No statistically significant increase in heritable effects has **ever** been observed in humans. Therefore, heritable disease risk estimates are extrapolated from animal data.
- **UNSCEAR Report 2001**
  - Heritable disease risk of **0.41–0.64%/Gy** per child of an individual irradiated at low dose rate and low LET.
  - Risk increases to **0.53–0.91%/Gy** per child if second-generation (grandchildren) are included.
  - Heritable disease risk is probably higher for high dose rate and high LET, but not high enough to be directly observed in atomic bomb survivors.
  - The population risk is lower than the per-child risk because some people have already finished having children, or will never have children.
- The **UNSCEAR** estimate for heritable damage after large-population radiation exposure is:
  - **0.2%/Gy** for the entire population.
  - **0.1%/Gy** for the working population.
- Note that **heritable damage risk** is a function of **gonadal dose** only. It does not matter how much dose is absorbed by the brain, breasts, lung, rectum, etc.

Genetic Risks and Radiation Therapy

- Sperm production is lost after **3.5–8 Gy**, while ovarian function is lost after **2–12 Gy** depending on age.
  - Older women = closer to menopause = less dose required to induce menopause.
- **Sperm** takes 2–3 months to mature, so there is a delay between testicular irradiation and loss of fertility.
  - Infertility occurs at much lower doses than hormonal changes (hypogonadism).
- **Ovarian failure** occurs immediately after radiation and includes all of the hormonal symptoms of menopause (no hormonal changes associated with male sterility).
- Doses of radiation insufficient to prevent fertility may increase the risk for heritable disease by approximately **0.53–0.91%/Gy**.
- Based on mouse data, waiting at least 6 months between irradiation and conception may decrease this risk, although some genetic risk may persist indefinitely.

Radiation Protection Guidelines

- These rules and regulations are designed to limit radiation risk to the public, to radiation workers, and to children/fetuses.
- The permissible dose limits vary between nations and different councils, and depend on the exposed tissue and population (e.g., radiation worker vs. members of the general public, e.g., the "individual").
- The **US NCRP** regulations give dose limits for individuals or workers (and in the latter case, areas of work [controlled vs. uncontrolled]), and for areas of the body:
- **Individual Annual Dose Limits**
  - **Radiation Worker, Infrequent Exposure**:
    50 mSv total body, 50 mGy lens (see above), **500 mSv** other single organ.
  - **General Public, Infrequent Exposure**:
    5 mSv total body, 15 mGy lens (see above), **50 mSv** other single organ.
  - **General Public, Continuous Exposure**:
    1 mSv total body
  - **Embryo/Fetus**:

0.5 mSv/month, once pregnancy has been declared

- **Area Dose Limits**
  - **Uncontrolled Area: ≤0.02 mSv/h** AND **≤ 0.1 mSv/week**.
    At the maximum dose rate of 0.02 mSv/h, the area can only be occupied for 5 hour a week without exceeding the weekly limit.
  - **Controlled Area: ≤1 mSv/week**.

Some Take-Home Points and Other Numbers to Remember

- **Carcinogenesis risk** and **heritable damage risk** are both considered **stochastic effects**; as far as anyone knows there is no "safe" threshold dose.
- **Equivalent dose (Sv)** is weighted for radiation type.
- **Effective dose (Sv)** is weighted for both radiation type and tissue irradiated.
- **Dose and dose rate effectiveness factor (DDREF)** is defined as either "low" or "high":
  - **Low DDREF** = Low LET radiation with either dose < 0.2 Gy, or dose rate < 0.1 Gy/h.
  - **High DDREF** = Low LET dose > 0.2 Gy and dose rate > 0.1 Gy/h, or High LET radiation at any dose and dose rate.
- The **radiation-induced malignancy risk** is calculated using **effective dose (Sv)**:
  - **10%/Sv** for entire population and **high DDREF**.
  - **8%/Sv** for working population and **high DDREF**.
  - **5%/Sv** for entire population and **low DDREF**.
  - **4%/Sv** for working population and **low DDREF**.

- The **heritable damage risk** is calculated using **gonadal dose (Gy)**:
  - **0.41–0.64%/Gy/child** of an irradiated individual.
  - **0.2%/Gy/individual** for the entire population.
  - **0.1%/Gy/individual** for the working population.
  - Mouse data suggest that waiting a number of months between irradiation and conception may decrease the risk of heritable damage.

Radiation Effects in the Embryo and Fetus

35

Introduction

The severity of the effects of ionizing radiation on the pre- and postimplantation embryo/fetus is dependent upon the dose, dose rate, and stage of gestation. In the preimplantation (conceptus) stage, relatively low doses of radiation may result in death; in surviving embryos, malformations are unlikely. During organogenesis, radiation may cause severe organ malformations along with the possibility of fetal death or growth retardation. During the fetal growth stage, radiation may cause permanent growth retardation, mental retardation, and microcephaly. Prenatal radiation may also cause radiation-induced carcinogenesis at a rate higher than what is expected in children or adults.

Stages of In Utero Development

- **Preimplantation (conceptus)**: Limited number of cells, no differentiation.
  - **Days 0–5** in mice, **Weeks 0–2 (Days 0–9)** in humans.
- **Organogenesis (embryo)**: Cells begin to differentiate into organs and tissues.
  - **Days 5–13** in mice, **Weeks 2–6 (Days 10–42)** in humans.
- **Fetal Growth (fetus)**: Structures are formed, and only need to grow and mature.
  - **Days 13–20** in mice, **Weeks 6–40** in humans (Fig. 35.1).

Of Mice and Men

- The mouse is the most common experimental animal for gestational defects.
- In mice, the **conceptus**, **embryo**, and **fetal** stages are roughly equal in length, with full-term gestational period of **20 days**.
- In man, the **fetal** stage is overwhelmingly longer, comprising the majority of the **9 months**.

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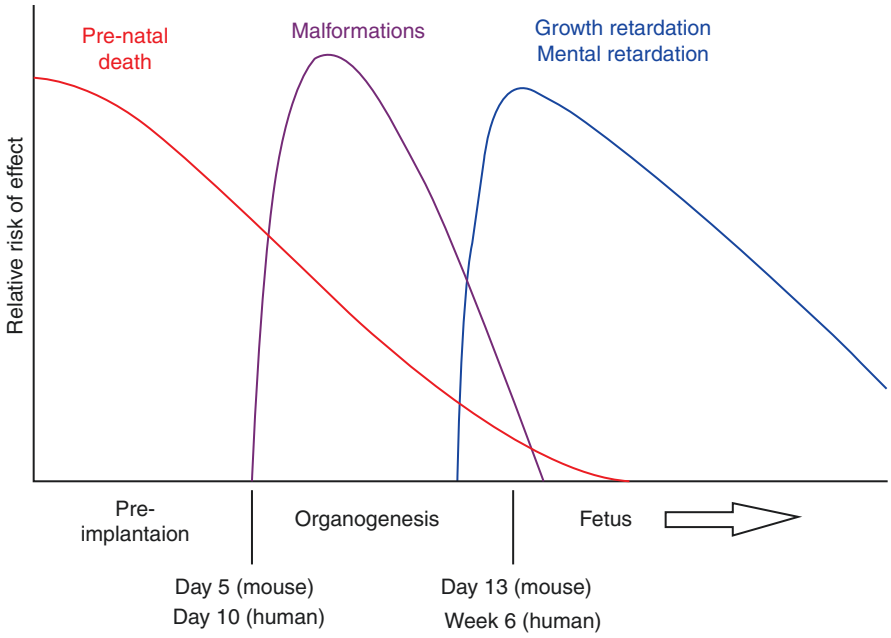

Fig. 35.1 Relative risk of various effects of ionizing radiation administered during specific phases of intrauterine development

- Mice appear to be more susceptible to organ malformations while humans appear to be more susceptible to growth retardation and mental retardation.

Preimplantation Damage: All or Nothing

- The preimplantation **conceptus** has the highest radiosensitivity; **0.05–0.15 Gy** can cause significant killing.
- Damage has an **all-or-nothing** effect:
  - Mild damage is completely repaired, no abnormalities are seen because cells at this stage are pluripotent stem cells so if one cell dies from radiation others can survive and the embryo can develop normally.
  - Significant damage results in failure to implant. At this early stage, the pregnancy is likely to go undetected.
- Atomic bomb survivor data show a deficit in children born after radiation exposure at **0–4 weeks** gestational age, implying a high rate of prenatal death.
  - However, children irradiated between **0 and 2 weeks** gestational age did not have an elevated rate of abnormalities.

Embryonic Damage: Malformations

- The embryo is extremely sensitive to radiation, with a dose of **1 Gy** resulting in a **100% rate of severe malformations** in rats.
  - In contrast, human A-bomb data did not show any excess malformations. However, therapeutic doses of pelvic irradiation did cause gross malformations.
- Damage is related to organ formation:
  - Neural tube defects – Anencephaly, craniocele, meningocele, etc.
  - Coelomic defects – Evisceration, intestinal malformations.
  - Cardiac, pulmonary, renal, genitourinary, ophthalmic, bone/joint, etc.
  - Limb bud formation defects, see example (Fig. 35.2)

- **Temporary growth retardation** occurs in animals, with growth catching up after birth if they are irradiated during the period known as "major organogenesis."
  - This phenomenon does not appear to happen in humans. Low birth weight correlates with small adult height and weight.
- Very likely to cause intrauterine or neonatal death.

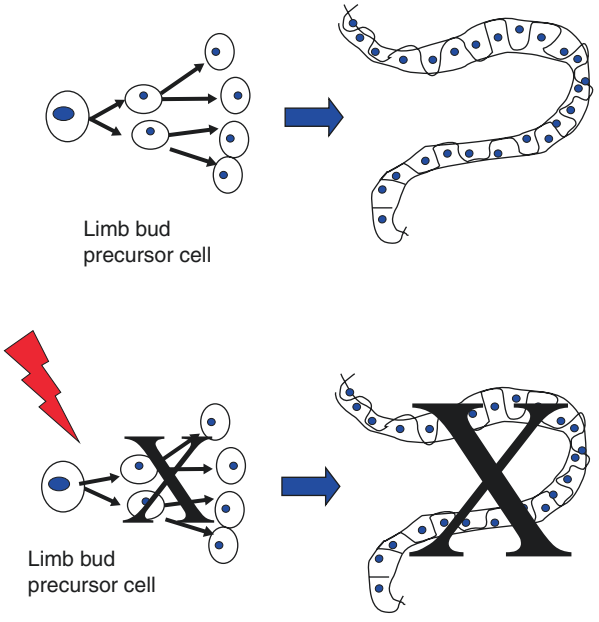

Fig. 35.2 Radiation-induced limb bud defects during organogenesis. Embryonic cells in the blastula stage are differentiating. Defects are most apparent when the specific cell of an organ "to be" such as limb bud cells are killed by radiation exposure

Fetal Damage: Organ Growth Defects

- The fetus is much less sensitive to radiation compared to the conceptus and embryo. Damage primarily decreases organ size.
  - Doses of **0.1 Gy** and above are required to produce a measurable effect.
- Radiation kills a fraction of cells in the growing fetus, leading to permanent decrease in size.
  - **Permanent growth retardation**: Low birth weight and small adult height/weight can result during irradiation during the "fetal stage."
  - **Mental retardation**: Due to decreased number and migration of neurons and glia.
  - **Microcephaly** (humans): Combination of overall growth retardation and low brain size. May occur even in the absence of mental retardation.
- Radiation effects depend on the time of irradiation.
- In **A-bomb survivors** exposed in utero:
  - **0–7 weeks postconception**: Growth retardation and microcephaly, with or without mental retardation.
  - **8–15 weeks postconception**: Most sensitive phase for mental retardation, approximately **25 IQ/Gy**. Severe growth retardation and microcephaly.
  - **16–25 weeks postconception**: Mild-to-moderate mental retardation, minimal-to-mild growth retardation. However, there is possibly a threshold for mental retardation at lower doses.
  - **26+ weeks postconception**: Much less likely to cause severe defects.
  - No excess of organ malformations was observed.
  - Severe mental retardation noted between 8 and 25 weeks postconception.

Prenatal Radiation and Carcinogenesis

- Data come from **obstetric X-rays** in the 1950s.
  - Very low dose (**2.0–4.6 mGy**) compared to A-bomb or therapeutic irradiation experience.
  - Majority of radiation exposures occurred in the third trimester of pregnancy. (**26+ week gestational age**).
- Approximately, **40%** increased **relative risk** in childhood cancers with an obstetric X-ray.
- **Absolute risk** estimate (Doll and Wakeford) is **6%/Gy** for low-dose fetal irradiation, which is only slightly higher than the **ICRP 4%/Sv** for adults and **5%/Sv** for the general public.
- **Prenatal fetal irradiation has been shown to induce DNA damage and mutations in mice and hamsters and may help explain the increase in cancer risk observed.**

Therapeutic Radiation in Pregnancy

- **Goldstein and Murphy (1929)** studied the children of 38 women who were treated with therapeutic radiation (such as for cervical cancer) while pregnant.
  - The fetal doses were poorly defined as they did not have accurate dosimetry in 1929.
  - However, the radiation doses were certainly much higher than the doses from A-bomb or diagnostic X-ray series.
    Presumably closer to 45 Gy than 1 Gy.
- Multiple malformations were reported including spina bifida, clubfeet, skull defects, hydrocephaly, alopecia, limb defects, and blindness.
- Irradiation prior to **3 weeks** was unlikely to produce malformations, more likely to cause abortion.
- Irradiation between **4 and 11 weeks** gestational age was most likely to produce severe **malformations**.
- Irradiation between **11 and 16 weeks** produced **severe mental retardation** and growth retardation, and mild malformations.
- Irradiation after **16 weeks** produced **mild mental retardation** and growth retardation.
- Irradiation after **30 weeks** produced no gross abnormalities.
- This all matches up quite well with the theoretical and animal models.

Appendixes

Appendix A: Glossary of Terms and Physical Constants

Basic Physics and Radioactive Decay (Chaps. 1, 2, 3, 4, and 5)

°	Degrees
A	Activity (of a nuclide), or amplitude (of a wave), or atomic mass number (number of nucleons), or amperes (current) A_0 initial activity
α (alpha)	Alpha particle, 2 neutrons and 2 protons
β (beta)	Beta particle, an electron or positron β^- Electron β^+ Positron
Bq	Becquerel, one disintegration per second 10^6 = mega- (MBq) 10^9 = giga- (GBq)
c	Speed of light in a vacuum, 3×10^8 m/s
C	Coulombs, or carbon atom
°C	Degrees Celsius
Ci	Curie, 3.7×10^{10} disintegrations per second 10^{-6} = micro- (μCi) 10^{-3} = milli- (mCi)
d	Distance, or deuteron
D	Dose D_0 initial dose
Da	Dalton (atomic mass units) 1 Da = 931.5 MeV/c^2
e	Electron or positron, also the elementary charge, 1.602×10^{-19} C e^- Electron e^+ Positron
e^x	Natural exponent
E	Energy $E = mc^2$ equivalent energy of a mass m $E = h\nu$ energy of a photon with wavelength ν

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eV	Electron-volt, 1.602×10^{-19} J 10^{3} = kilo- (keV) 10^{6} = mega- (MeV) 10^{9} = giga- (GeV)
f	Roentgens-to-rads conversion factor
γ (gamma)	Gamma ray, a photon
Gy	Gray 10^{-6} = micro- (μGy) 10^{-3} = milli- (mGy) 10^{-2} = centi- (cGy) = 1 rad
h	Planck's constant, 6.62×10^{-34} J-s or 4.132×10^{-15} eV-s
H	Hydrogen H^{+} proton
hν (h-nu)	Photon, or the energy of a photon
hr	Hour
IR	Ionizing radiation
J	Joules
°K	Degrees kelvin
KERMA, or K	Kinetic energy released in media
LET	Linear energy transfer
λ (lambda, lowercase)	Decay constant
m	Mass, or meters 10^{-9} = nano- (nm) 10^{-6} = micro- (μm) 10^{-3} = milli- (mm) 10^{-2} = centi- (cm) 10^{3} = kilo- (km)
mc^2	Energy equivalent of a mass Rest mass of electron = 0.511 MeV Rest mass of neutron = 939.55; 939.55 MeV Rest mass of proton = 938.26 MeV
mgRaEq	Milligrams radium equivalent
Min	Minutes
μ (mu)	Attenuation coefficient
n	Neutron
N	Number of neutrons, or any generic "number"
N_A	Avogadro's number = 6.022×10^{23}
ν (nu)	Frequency, or neutrino
p	Momentum, or proton
P	Pressure, or phosphorous Standard pressure = 101.33 kPa = 1 atm
ϕ (phi)	Fluence
ψ (psi)	Flux (= energy * Fluence)
Q	Charge
r	Radius
Rad	cGy 10^{-3} = milli- (mrad) 10^{3} = kilo- (krad)
R	Roentgen, 2.58×10^{-4} C/kg 10^{-3} = mill- (mR)
R, R_{CSDA}	Range, continuous slowing down approximation
RBE	Relative biological effectiveness

ρ (rho)	Mass density
s	Seconds 10^{-9} = nano- (ns) 10^{-6} = micro- (μs) 10^{-3} = milli- (ms)
Sv	Sievert 10^{-6} = micro- (μSv) 10^{-3} = milli- (mSv)
t	Time $t_{1/2}$ half-life τ (tau) or t_{avg} mean life
T	Temperature Standard temperature = 295.15 K = 22 °C
v or V	Velocity
V	Volt, or volume
W	Energy per ion pair (in eV)
X	Exposure
yr	Year
Z	Atomic number, number of protons

Dose Specification and Calculation (Chaps. 6, 7, 8, 9, 10, and 11)

A	Activity
BSF	Backscatter factor (a component of TAR)
CT	Computed tomography
d	Depth, or distance d_{max} = depth of maximum dose
D	Dose D_{max} = maximum dose $\dot{D}$ Dose rate D_0 Initial dose
f	Roentgens-to-rads conversion factor
F	Mayneord F-factor
F(r,θ)	Anisotropy factor (for brachytherapy line sources)
g(r)	Radial dose function (for brachytherapy sources)
G(r,θ)	Geometry factor (for brachytherapy line sources)
Γ (gamma)	Exposure rate constant (for brachytherapy sources)
HDR	High dose rate brachytherapy
HVL	Half-value layer
I	Intensity I_0 = initial intensity
ISF	Inverse Square factor = $1/r^2$
K	Calibration factor (cGy/MU)
KERMA, or K	Kinetic energy released in media
kVp	Kilovolts peak
LDR	Low dose rate brachytherapy
λ (lambda, lowercase)	Decay constant
Λ (lambda, uppercase)	Dose rate constant
mAs	Milliamp-seconds
MDR	Medium dose rate brachytherapy

mgRaEq	Milligrams radium equivalent 1 mgRaEq = 8.25 R/cm²/h (exposure rate at 1 cm)
MLC	Multi-leaf collimator
MU	Monitor units
ODI	Optical distance indicator
OF	Obliquity factor
PDD	Percent depth dose
PDR	Pulse dose rate brachytherapy
RT	Radiotherapy
S_c	Collimator scatter factor
S_K	Air kerma strength
S_p	Phantom scatter factor
SABR	Stereotactic ablative radiotherapy
SAD	Source-axis distance SAD setup A treatment setup that uses constant SAD
SAR	Scatter-air ratio (a component of phantom scatter and TAR)
SOBP	Spread out Bragg peak
SSD	Source-skin (surface) distance SSD setup A treatment setup that uses constant SSD
TAR	Tissue-air ratio
TBI	Total body irradiation
TF	Tray factor (for photon dose calculations)
TMR	Tissue-maximum ratio (for photon dose calculations)
TPR	Tissue-phantom ratio (for photon dose calculations)
TV	Treated volume (volume receiving high dose)
TVL	Tenth-value layer
U	Unit (of air kerma strength)
WF	Wedge factor (for photon dose calculations)
X	Exposure $\dot{X}$ Exposure rate

Radiation Treatment Planning (Chaps. 9 and 12)

AP	Anteroposterior beam
BEV	Beam's eye view
CBCT	Cone beam computed tomography
CT	Computed tomography
CTV	Clinical target volume = GTV + margin for microscopic spread
d	Single fraction dose (compared to D as total dose)
D	Total dose (may include multiple fractions)
DRR	Digitally reconstructed radiograph = 2D image generated from 3D data
DVH	Dose-volume histogram
EBRT	External beam radiotherapy
EPID	Electronic portal imaging device
FoV	Field of view (for CT or MR imaging)
GTV	Gross tumor volume
HU	Hounsfeld units

IDL	Isodose line
IM	Internal margin = margin for internal motion and deformation
IMRT	Intensity modulated radiotherapy
ITV	Internal target volume = CTV + IM
IV	Irradiated volume = volume receiving low dose
mAs	Milliampere-seconds
MC	Monte Carlo (treatment planning algorithm)
MR, MRI	Magnetic resonance, magnetic resonance imaging
OAR	Organ at risk
ODI	Optical distance indicator
PA	Posteroanterior beam
PACS	Picture archiving and communication system
PET	Positron emission tomography
PRV	Planning risk volume = OAR + margin
PTV	Planning target volume = (CTV or ITV) + SM
RT	Radiotherapy
SABR	Stereotactic ablative radiotherapy
SBRT	Stereotactic body radiotherapy
SM	Setup margin = uncertainty in patient positioning and machine precision
SRS	Stereotactic radiosurgery
TBI	Total body irradiation
TPS	Treatment planning system
TV	Treated volume = volume receiving high dose
US	Ultrasound (imaging)
VMAT	Volumetric modulated arc therapy (a subtype of IMRT)

Radiation Protection and Quality Assurance (Chaps. 14, 15, and 16)

α	Scatter fraction (for secondary scatter)
B	Barrier factor
F	Beam area factor (for secondary scatter)
HVL	Half-value layer
MOSFET	Metal oxide semiconductor field effect transistor
OSLD	Optically stimulated luminescent dosimeter
P	Permissible dose
QA	Quality assurance Radiation protection and quality assurance
QAC	Quality assurance committee
QMP	Qualified medical physicist
RSO	Radiation safety officer
T	Occupancy factor
TLD	Thermoluminescent dosimeter
TVL	Tenth-value layer
U	Use factor
W	Workload
W_R	Weighting factor (for different types of radiation)

Molecular Biology (Chaps. 19, 20, 21, 24, 25, and 27)

46XX	A normal female karyotype with 46 total chromosomes, 44 autosomes and XX sex chromosomes
46XY	A normal male karyotype with 46 total chromosomes, 44 autosomes and XY sex chromosomes
A	Adenine, a purine base in DNA and RNA
BER	Base excision repair, repairs non-bulky base damage
bp or BP	Base pair (DNA)
C	Cytidine, a pyrimidine base in DNA and RNA.
cDNA	Complementary DNA, DNA reverse-transcribed from RNA for analysis.
DNA	Deoxyribonucleic acid
DSB	Double strand break (in DNA)
FISH	Fluorescence in situ hybridization, a technique for visualizing DNA and/or proteins
G	Guanine, a purine base in DNA and RNA.
G_0	Gap phase 0, occurs in non-dividing cells
G_1	Gap phase 1, occurs prior to S phase
G_2	Gap phase 2, occurs after S phase
GF	Growth fraction, the percentage of observed cells that are actively cycling.
GSH	Glutathione, reduced form (an active anti-oxidant)
GSSG	Glutathione, oxidized form (a used anti-oxidant)
HR	Homologous recombination repair, repairs DSBs
HSP	Heat shock protein
λ (lambda)	Cell distribution correction factor, always between 0.5 and 1
LI	Labeling index, the % of observed cells in S phase
LoH	Loss of heterozygosity, deletion of part of a chromosome.
M	Mitosis phase, nuclear and cell division occurs
MI	Mitotic index, the % of observed cells in M phase
MMR	Mismatch repair, repairs DNA mismatches and cross-links.
MSI	Microsatellite instability
NER	Nucleotide excision repair, repairs bulky base damage
NHEJ	Non-homologous end joining, repairs DSBs
O	Oxygen
−OH	Hydroxyl group, part of a larger molecule
−OOH	Peroxide group, highly reactive and damaging to larger molecules
ϕ (phi)	Cell loss fraction, the percentage of newly produced cells that die or senesce
−P	Phosphate group (PO_4), part of a larger molecule
PI	Propidium iodide, a dye used to stain DNA
RNA	Ribonucleic acid
RTK	Receptor tyrosine kinase
S	Synthesis phase, DNA is replicated
SSB	Single strand break (in DNA)
T	Thymine, a pyrimidine base in DNA
T_C	Total cell cycle time
T_{G1}	G_1 phase time
T_S	S phase time
T_{G2}	G2 phase time
T_M	M phase time
TK	Tyrosine kinase, may be a receptor or non-receptor
TKI	Tyrosine kinase inhibitor
U	Uracil, a pyrimidine base in RNA
X	X-chromosome
Y	Y-chromosome

Cell Survival Assays and Models (Chaps. 22 and 23)

α (alpha)	The linear component of linear-quadratic cell kill
β (beta)	The quadratic component of linear-quadratic cell kill
γ (gamma)	The slope of the tumor control dose-response curve
BED	Biologically effective dose, or biologically equivalent dose (EQD is preferred for equivalent dose)
CHO	Chinese hamster ovary cell line
d	Dose per fraction
D	Total dose
D_0 (D-zero or D-not)	Additional radiation dose that reduces cell survival to 0.37× its previous value
D_{10} (D-ten)	Additional radiation dose that reduces cell survival to 0.1× its previous value
D_{prolif}	Daily dose required to counteract proliferation
D_q	Quasithreshold dose, the "shoulder width" of a survival curve
DRF	Dose reduction factor (of a radioprotector)
EQD	(biologically) Equivalent dose
ER	Enhancement ratio (of a radiosensitizer)
$Gy_{3,2}$	Gy of biologically equivalent dose with α/β ratio of 3 Gy and a fraction size of 2 Gy
Gy_2	Gy of biologically effective dose with α/β ratio of 2 Gy
H_2	Thames H-factor for 2 fractions per day
HeLa	Human cell line (Henrietta Lacks)
LQ, or L-Q	Linear quadratic survival model
n, or N	Number of fractions
NSD	Ellis normalized standard dose
NTCP	Normal tissue complication probability
OER	Oxygen enhancement ratio
PE	Plating efficiency
PLDR	Potentially lethal damage repair
RBE	Relative biological effectiveness
SF	Surviving fraction
SLDR	Sublethal damage repair
T	Time
TCD_{50}	Tumor control dose 50, radiation dose causing a 50% probability of tumor control
TCP	Tumor control probability
TD_{50}	Tolerance dose 50, radiation dose causing a 50% probability of toxicity
TD_{50}	Tumor dilution 50, number of tumor cells required to cause a tumor in 50% of experimental animals
Tk	Kickoff time, delay between start of treatment and start of accelerated repopulation
TR	Therapeutic ratio

Macroscopic Biology (Chaps. 25, 28, 30, 34, 34, and 35)

BID	Twice daily
BNCT	Boron neutron capture therapy
CEM 43°	Cumulative equivalent minutes at 43 °C, a measure of thermal dose
CNS	Central nervous system

CTC-AE	Common Toxicity Criteria for Adverse Events, a toxicity grading schema
DDREF	Dose and dose-rate effectiveness factor
FSU	Functional subunit
GI	Gastrointestinal
HD	Hodgkin disease (lymphoma)
HLA	Human leukocyte antigen (used to match transplant donor and recipient)
HSC	Hematopoietic stem cell(s)
HSCT	Hematopoietic stem cell transplant
LD_{50}	Lethal dose 50, radiation dose causing a 50% probability of lethality $LD_{50/60}$ lethal dose 50 at 60-day follow-up
LENT-SOMA	Late Effects of Normal Tissue, Subjective and Objective Management Analytic, a toxicity grading schema
LNT	Linear no-threshold model of carcinogenesis
RBC	Red blood cell(s)
TBI	Total body irradiation
TER	Thermal enhancement ratio
TID	Three times daily
WBC	White blood cell(s)
WF	Weighting factor, equivalent to W_R for radiation protection

List of Biomolecules

AR	Androgen receptor, a nuclear receptor
ATM/ATR	Part of the DSB detection pathway
Bcl-2, Bcl-XL	Pro-survival, anti-apoptosis genes
bFGF	Basic fibroblast growth factor
BRCA1/2	Homologous recombination repair genes, implicated in hereditary breast and ovarian cancer
Cdk	Cyclin dependent kinase cdk4/6, cdk2, cdk1
Cdki	Cyclin dependent kinase inhibitors
Chk1/2	Cell cycle checkpoint molecules, promote cell cycle arrest
Cyclins	Cell cycle regulatory molecules, associated with cdks Cyclin D, E, A, B
Cyt c	Cytochrome c, an energy producing mitochondrial molecule that causes apoptosis if it enters the cytoplasm
E6/E7	Viral genes carried by HPV, they inhibit p53 and cause squamous cell cancers
EBV	Epstein-Barr virus, responsible for infectious mono and nasopharyngeal cancer
EGF	Epidermal growth factor
EGFR family	EGF receptors, membrane bound receptor tyrosine kinases targeted by multiple drugs EGFR/Her1/ErbB1 EGFR2/Her2/ErbB2 Her3/ErbB3 Her4/ErbB4
ER	Estrogen receptor, a nuclear receptor
HIF1	A hypoxia signaling molecule, includes HIF1α and HIF1β

HPV	Human papillomavirus. High risk subtypes are responsible for all cervical cancers and many head and neck cancers
HSP	Heat shock protein
IFNα and other IFNs	Interferons, a family of pro-inflammatory cytokines
IL-1 and other IL-s	Interleukins, a family of pro-inflammatory cytokines
MLH/MSH/PMS family	Mismatch repair genes, defects cause Lynch syndrome
MRE/rad50/NBS1 (MRN complex)	Part of the DSB signaling pathway
NFkβ	A pro-inflammatory, pro-survival molecule found in hypoxia, angiogenesis and invasion
p15/p16(INK4A)	Cell cycle inhibitors, inhibit cyclin
p53	A DNA damage response gene, inhibits the cell cycle and encourages apoptosis
PR	Progesterone receptor, a nuclear receptor
RAR/RXR	Retinoid receptors, nuclear receptors
TGFβ	Transforming growth factor beta, a pro-inflammatory molecule
TNFα	Tumor necrosis factor alpha, a pro-inflammatory molecule.
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptors, membrane bound receptor tyrosine kinases, targeted by multiple drugs
VHL	The von Hippel Lindau gene, degrades HIF1α. Defects cause von Hippel Lindau syndrome, multiple tumors including renal cell CA
XP family	Nucleotide excision repair genes, defects cause xeroderma pigmentosum

List of Drugs

^{18}FDG	Radiolabeled glucose for PET imaging
^{3}H-thymidine	Radiolabeled thymidine for S phase imaging
5-FU	A nucleoside analogue chemotherapy drug
ALA	Aminolevulinic acid, a drug used in photodynamic therapy
Amifostine	A sulfhydryl radioprotector
Anastrozole	An aromatase inhibitor anti-estrogen
BrdU or BUdR	Bromodeoxyuridine, a nucleoside analogue radiosensitizer, also used for S-phase staining
Busulfan	An alkylating chemotherapy drug
Capecitabine	A chemotherapy prodrug that produces 5-FU
Carbogen	A gas mixture of 95% O_2 and 5% CO_2 used as oxygen modifying therapy
Cetuximab	An anti-EGFR1 monoclonal antibody
Cisplatin, Carboplatin, Oxaliplatin	Platinum chemotherapy drugs, cross-links DNA
Cyclophosphamide (Cytoxan)	A nitrogen mustard chemotherapy drug, alkylating agents
Docetaxel	See paclitaxel
Doxorubicin (Adriamycin), Daunorubicin, other “rubicins”	Anthracycline-class chemotherapy drugs, intercalates in DNA
Erlotinib	An anti-EGFR tyrosine kinase inhibitor
Etanidazole	A nitroimidazole hypoxic radiosensitizer

Etoposide	A topoisomerase poison chemotherapy drug
Gemcitabine	A nucleoside analogue chemotherapy drug
Goserelin	A LHRH-analogue anti-hormonal therapy
HBO_2	Hyperbaric oxygen, used as oxygen modifying therapy and for wound healing
HU	Hydroxyurea, a S-phase specific toxin
Ifosfamide	An alkylating chemotherapy drug
Irinotecan	A topoisomerase poison chemotherapy drug
IUdR	Iododeoxyuridine, a nucleoside analogue radiosensitizer
Leuprolide	A LHRH-analogue anti-hormonal therapy
Melphalan	An alkylating chemotherapy drug
Methotrexate	An anti-folate chemotherapy drug
Misonidazole	A nitroimidazole hypoxic radiosensitizer
MMC	Mitomycin C, a chemotherapy drug and hypoxic cytotoxin
Nicotinamide	A vasodilator used as oxygen modifying therapy
Nimorazole	A nitroimidazole hypoxic radiosensitizer
Paclitaxel, Docetaxel and other "taxel"s	Taxane-class chemotherapy drugs, microtubule toxins
Pimonidazole	A nitroimidazole hypoxic radiosensitizer
Rituximab	An anti-CD20 monoclonal antibody
Sorafenib, Sunitinib	Multi-specific tyrosine kinase inhibitors
Tamoxifen	A selective estrogen receptor modulator
Temozolomide	An alkylating chemotherapy drug
Tirapazamine	A hypoxic cytotoxin
Trastuzumab	An anti-Her2 (EGFR2) monoclonal antibody
Vincristine, vinblastine and other "vin-"s	Vinca alkaloids, microtubule toxin chemotherapy drugs

Organizations and Standards

AAMD	American Association of Medical Dosimetrists
AAPM TG-000	AAPM Task Group Report #000
AAPM	American Association of Physicists in Medicine
ABR	American Board of Radiology
ACR	American College of Radiology
ADCL	Accredited Dosimetry Calibration Laboratory
ASTRO	American Society for Radiation Oncology
BEIR	Biological Effects of Ionizing Radiations (reports)
CERN	European Organization for Nuclear Research (Conseil Européen pour la Recherch Nucléaire)
DICOM	Digital Imaging and Communications in Medicine
DOT	Department of Transportation
FDA	Food and Drug Administration
ICRP	International Commission on Radiation Protection
ICRU	International Commission on Radiation Units

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCRP	National Council on Radiation Protection and Measurements
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NRC	Nuclear Regulatory Commission
RTOG	Radiation Therapy and Oncology Group
SI	International System of Units (Systeme International d'unites)
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation

Appendix B: List of Radionuclides for Radiotherapy and Imaging

Listed in Order from Heaviest to Lightest

Sealed sources		Origin	Energy	Half-life
^{226}Ra	Radium	Uranium decay (^{238}U)	0.83 MeV gamma	1601 years
^{222}Rn	Radon	Uranium decay (^{226}Ra)	0.83 MeV gamma	2.7 days
^{198}Au	Gold	Neutron bombardment	0.411 MeV gamma	2.7 days
^{192}Ir	Iridium	Neutron bombardment	0.38 MeV gamma	74 days
^{137}Cs	Cesium	Fission by-product	0.662 MeV gamma	30 years
^{131}Cs	Cesium	Fission by-product	30 keV X-ray	9.7 days
^{125}I	Iodine	Neutron bombardment	28 keV X-ray	60 days
^{103}Pd	Palladium	Neutron bombardment	21 keV X-ray	17 days
^{60}Co	Cobalt	Neutron bombardment	1.25 MeV gamma	5.26 yrs
Unsealed sources		**Origin**	**Energy**	**Half-life**
^{223}Ra	Radium	Uranium decay (^{235}U)	6 MeV alpha	11.4 days
^{153}Sm	Samarium	Neutron bombardment	810 keV beta−	47 hr
^{177}Lu	Lutetium	Neutron or proton bombardment	490 keV beta−, 210 keV gamma	6.7 days
^{131}I	Iodine	Fission by-product	606 keV beta−, 364 keV gamma	8 days
^{90}Sr	Strontium	Fission by-product	546 keV beta−	29 yrs
^{90}Y	Yttrium	Daughter elution (^{90}Sr)	940 keV beta	50 days
^{89}Sr	Strontium	Neutron bombardment	583 keV beta−	50.5 days
^{32}P	Phosphorous	Neutron bombardment	695 keV beta−	14 days
Imaging nuclides		**Origin**	**Energy**	**Half-life**
^{123}I	Iodine	Proton bombardment	159 keV gamma	13 hr
^{111}In	Indium	Proton bombardment	208 keV gamma	2.8 days
^{99m}Tc	Technetium	Daughter elution (^{99}Mo)	140 keV gamma	6 hr
^{64}Cu	Copper	Daughter elution (^{64}Zn)	653 keV beta+	12.7 hr
^{18}F	Fluorine	Proton bombardment	630 keV beta+	110 min
^{15}O	Oxygen	Proton bombardment	1.73 MeV beta+	2 min
^{11}C	Carbon	Proton bombardment	960 keV beta+	20 min
^{3}H	Tritium	Neutron bombardment	19 keV beta−	12 yrs
^{68}Ga	Gallium	Daughter elution (^{68}Ge)	1.9 MeV beta+	68 min

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